

# **New strategies for the synthesis and functionalization of aliphatic amines**

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This dissertation is submitted for the Degree of Doctor of Philosophy

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### *Declaration*

This thesis is submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy. It describes the work carried out in the Department of Chemistry from October 2014 to April 2018. This dissertation is the result of my own work and includes nothing that is the outcome of work done in collaboration except where specifically indicated in the text.

Aaron D. Trowbridge

### *Statement of Length*

This thesis does not exceed the word limit of 60, 000 as set by the Degree Committee for the faculty of Physics and Chemistry

Aaron D. Trowbridge



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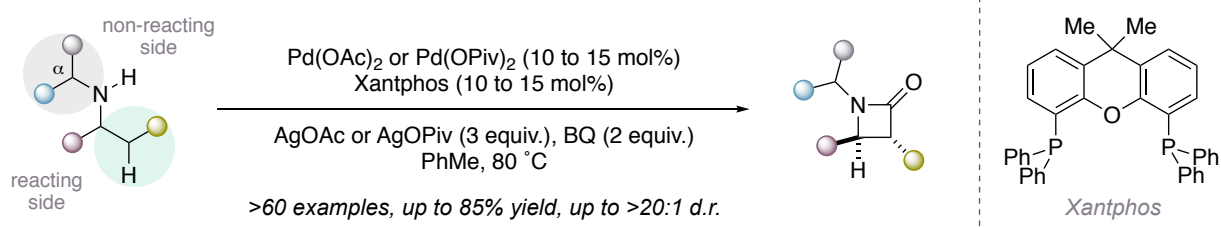
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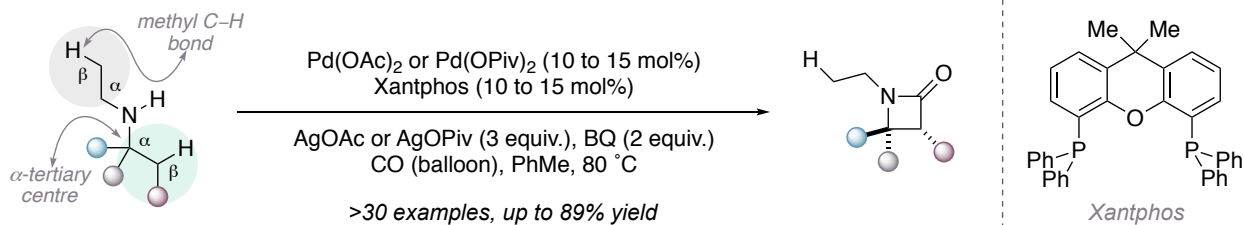
## Abstract

The invention of catalytic processes that convert feedstock chemicals into pharmacologically-privileged amines is a landmark challenge in organic synthesis. This thesis describes the development of three novel transition-metal catalyzed processes for the synthesis of alkylamines that attempts to meet this challenge.

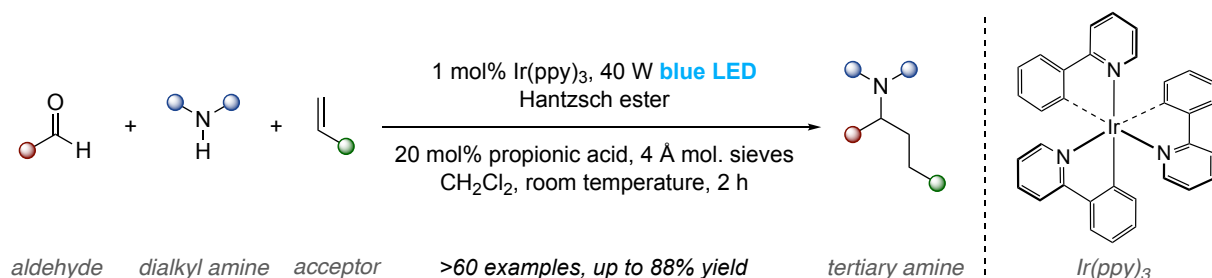
The first Pd-catalyzed methylene  $\beta$ -C–H carbonylation of alkylamines to form substituted  $\beta$ -lactams is reported. Through the synergistic use of a Pd-catalyst and Xantphos ligand, secondary amines underwent exclusive methylene  $\beta$ -C–H activation in high yields and diastereoselectivities.



Subsequently, the development of a remarkably selective methylene  $\beta$ -C–H carbonylation of  $\alpha$ -tertiary amines (ATAs), is detailed. This methodology enables the C–H carbonylation of methylene C–H bonds over traditionally more reactive methyl and  $\text{C}(\text{sp}^2)$ -H bonds. Importantly, a range of functional groups previously incompatible with C–H technologies were tolerated in good yields.



Finally, the development of a novel multicomponent synthesis of tertiary amines is described. The novel photocatalytic single-electron reduction of alkyl iminium ions furnishes  $\alpha$ -amino radicals that engage alkenes forming a new C–C bond. The reaction exhibits broad functional group tolerance and enables the synthesis of amines not readily accessible by existing methods.



## Abbreviations

Å	Angstrom
Ac	acetyl
acac	acetylacetonato
Ad	adamantyl
aq.	aqueous
Ar	aryl
An	4-methoxybenzyl
APAO	<i>N</i> -acetyl-protected aminomethyl oxazoline
Asc	ascorbic acid
ATA	$\alpha$ -tertiary amine
atm	atmosphere
BArF	tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
BDE	bond dissociation energy
BDFE	bond dissociation free energy
BINOL	1,1'-bi-2-naphthol
BisSO	1,2-bis(phenylsulfinyl)ethane
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
b.p.	boiling point
BPhen	bathophenanthroline
BTMG	2- <i>tert</i> -butyl-1,1,3,3-tetramethylguanidine
BTPP	biphenyl-2,2',6,6'-tetrakis(dipyrrolylphosphoramidite)
Bu	butyl
bpy	2,2'-bipyridine
BQ	benzoquinone
Bz	benzoyl
Bz <sup>F</sup>	pentafluorobenzoyl
C	Celsius
c	concentration
Cal	calories
CAN	ceric ammonium nitrate
cat	catalytic or catalyst
Cbz	carboxylbenzyl
CDI	carbonyldiimidazole
CFL	compact fluorescent lamp
cm <sup>-1</sup>	wavenumbers
CMD	concerted metallation-deprotonation
cod	1,5-cyclooctadiene
coe	cyclooctene
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
CSA	camphorsulfonic acid
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DCE	1,2-dichloroethane
dCype	1,2-bis(dicyclohexylphosphino)ethane
dCypm	bis(dicyclohexylphosphino)methane
dF	difluoro ( <i>in reference to photocatalysts</i> )
dfs	2,6-difluorophenoxy sulfonyl
DFT	density functional theory
DG	directing group
DHBQ	2,5-dihydroxy-1,4-benzoquinone
DIBAL-H	diisobutylaluminium hydride
DIPEA	<i>N,N</i> -diisopropylethylamine
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMBQ	2,6-dimethoxybenzoquinone
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMPU	<i>N,N'</i> -dimethylpropyleneurea
DMSO	dimethylsulfoxide
DNB	dinitrobenzene
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
DPPF	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
d.r.	diastereomeric ratio
dtbbpy	4,4'-di- <i>tert</i> -butyl-2,2'-bipyridine
DTBMP	2,6-di- <i>tert</i> -butyl-4-methylpyridine
$E_{1/2}$	half-wave potential
e.e.	enantiomeric excess
Et	ethyl
equiv	equivalent
ESI	electrospray ionisation
esp	$\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropioante
F	fluorescence intensity
<i>fac</i>	facial
FG	functional group
g	gram
GC-MS	gas chromatography-mass spectrometry
h	hour
HAA/HAT	hydrogen atom abstraction/transfer
HEH	Hantzsch ester
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HMDS	hexamethyldisilazide
HOMO	highest occupied molecular orbital
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
Int	intermediate
IR	infrared
<i>i</i>	iso
<i>J</i>	coupling constant
k	kilo

$k_q$	bimolecular quenching constant
L	neutral ligand or litre
LC-MS	liquid chromatography-mass spectrometry
LED	light emitting diode
Leu	leucine
LUMO	lowest unoccupied molecular orbital
$\mu$	micro
M	metal <i>or</i> molar <i>or</i> Markovnikov
<i>m</i>	meta
m	milli
<i>m</i> CPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
Meoc	methyloxycarbonyl
Mes	mesityl
MHz	megaHertz
MIA	2-methoxyiminoacetyl
mol	mole
m.p.	melting point
MPA	3-mercaptopropionic acid
MPAA	mono- <i>N</i> -protected amino acid
MQ	5-methoxyquinolinamide
Ms	methanesulfonyl
M.S.	molecular sieves
MTBE	methyl <i>tert</i> -butyl ether
<i>n</i>	normal
nbd	norbornadiene
neo	neopentyl glycolato
NFSI	<i>N</i> -fluorobenzenesulfonimide
NHC	<i>N</i> -heterocyclic carbene
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Ns	4-nitrobenzenesulfonyl
Nu(H)	nucleophile
<i>o</i>	ortho
ox	oxidation
<i>p</i>	para
PA	picolinamide or phosphoric acid
PCET	proton coupled electron transfer
PG	protecting group
Ph	phenyl
Ph-BPE	1,2-bis(2,5-diphenylphospholano)ethane
phen	phenanthroline
Phs	phenoxysulfonyl
Phth	phthalimido
PIDA	(diacetoxyiodo)benzene
Pin	pinacolato
Piv	pivaloyl
PMP	4-methoxyphenyl
ppm	parts per million
ppy	2-phenylpyridinato

Pr	propyl
PTSA	<i>para</i> -toluenesulfonic acid
Py	pyridine
PyBOX	2,6-bis(oxazolin-2-yl)pyridine
Q	quinolinamide or quencher
quant	quantitative
R	undefined group
R <sub>f</sub>	retention factor
rac	racemic
red	reduction
rt	room temperature
s	second
<i>s</i>	selectivity
sat	saturated
SCE	standard calomel electrode
SCX	strong cation exchange
Ser	serine
Ses	2-(trimethylsilyl)ethanesulfonyl
SET	single electron transfer
SM	starting material
SOMO	singularly occupied molecular orbital
sub	substituted
τ	excited state lifetime
<i>t</i>	tert
TBAA	tetra- <i>n</i> -butylammonium acetate
TBAI	tetra- <i>n</i> -butylammonium iodide
TBDMS	<i>tert</i> -butyldimethylsilyl
TBME	<i>see</i> MTBE
TC	thiophene-2-carboxylate
TCE	1,1,2,2-tetrachloroethene
Tces	2,2,2-trichloroethoxysulfonyl
TDG	transient directing group
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
Tf	trifluoromethanesulfonyl
TFE	2,2,2-trifluoroethanol
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMB	2,4,6-trimethylbenzyl
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TON	turn over number
TPA	triphenylacetate
TPP	tetraphenylporphyrin
TRIP	3,3'- <i>bis</i> (2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
Ts	tosyl
UV	ultra-violet
V	volt

Val	valine
vis	visible light
X	halogen <i>or</i> anionic ligand

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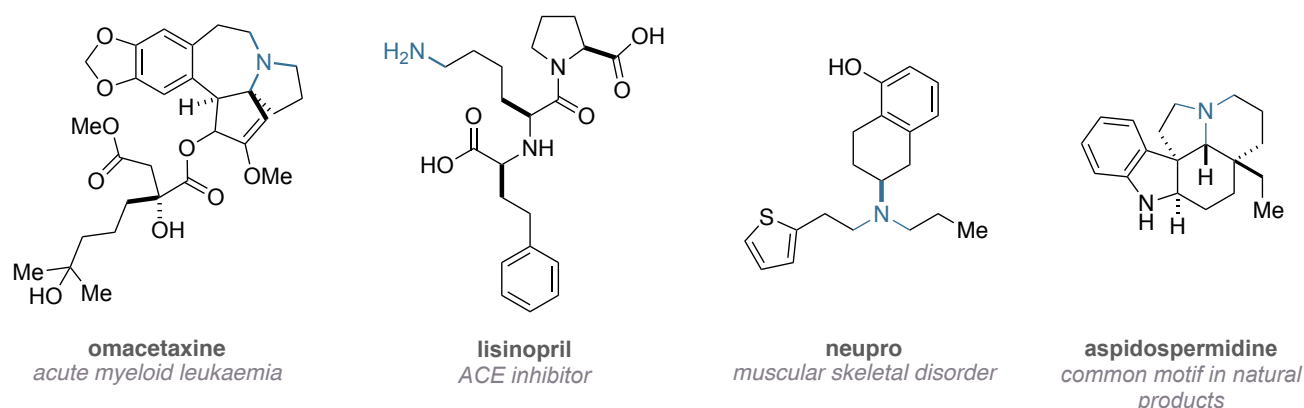


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# 1 Catalytic Methods for the Synthesis of Aliphatic Amines

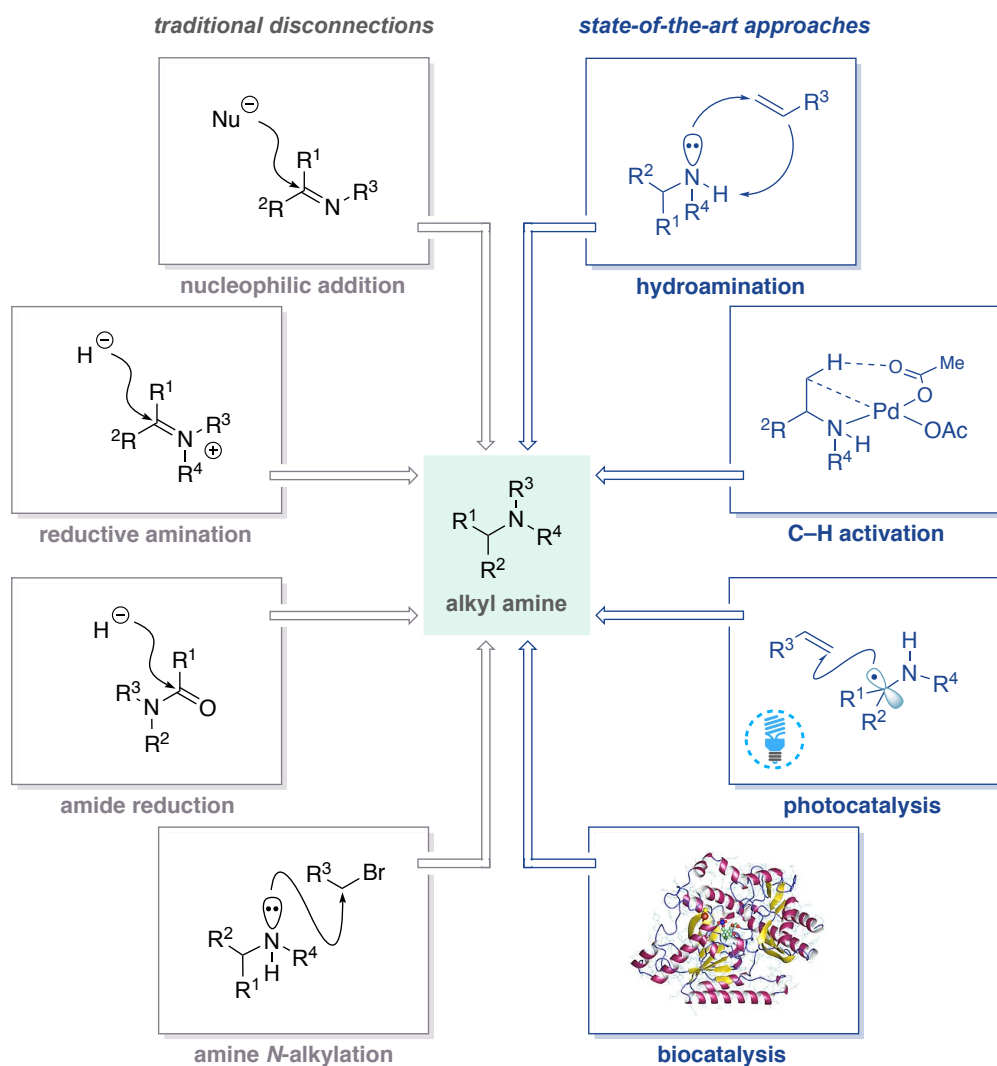
## 1.1 The evolution of amine synthesis

Aliphatic amines, wherein only *H* or *alkyl* substituents are connected to the nitrogen atom, are one of the most important functional groups in organic chemistry<sup>1</sup>. The groups appended to the nitrogen atom not only control the physical properties, but are also responsible for regulating key biological interactions<sup>2,3</sup>. In many cases, the nitrogen lone-pair effectively increases solubility while its substituents increase lipophilicity – a crucial feature in a molecule's ability to cross cell membranes and the blood-brain barrier<sup>4-6</sup>. As such, aliphatic amines are ubiquitous amongst pharmaceutical agents, small-molecule biological probes and pre-clinical candidates (Figure 1)<sup>7</sup>. Therefore, the ongoing need for new and complex amines through which to probe novel reactivity has driven the development of innovative chemical methods for their synthesis<sup>8</sup>.



**Figure 1** | The importance of alkylamines in pharmaceuticals

Despite the widespread significance of alkylamines, traditional methods for their synthesis can often be problematic due to low yields resulting from poor selectivity and harsh reaction conditions. Illustrated in Scheme 1 is a brief overview of the evolution of methods for the synthesis of alkylamines, from which appropriate conditions can be properly identified to synthesize the desired amine effectively. Without doubt, the methods of choice for the day-to-day synthesis of aliphatic amines are alkylation and carbonyl reductive amination<sup>7,9</sup>. In principle, direct *N*-alkylation, termed Hoffman alkylation after its first report by A. W. Hoffmann in 1850<sup>10</sup>, is the simplest and most convenient method for the synthesis of aliphatic amines<sup>11</sup>. The reaction between simple amines and alkyl (pseudo)halides, enables the direct construction of ‘higher order’ amine products.



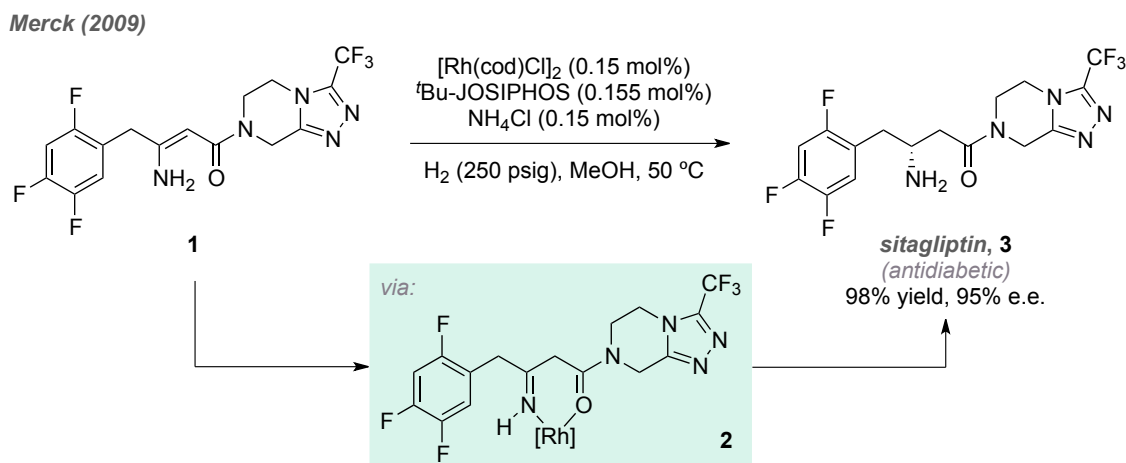
**Scheme 1** | Overview of the evolution of methods for the synthesis of alkylamines

Although direct *N*-alkylation has been routinely practiced for well over a century, it is widely acknowledged to suffer from issues of selectivity, resulting in poor atom-economy<sup>12</sup>. In spite of large excesses of amine, over-alkylation forming mixtures of secondary and tertiary amines, as well as ammonium salts, is commonplace – leading to tedious and costly separations<sup>13</sup>. Despite great efforts to curtail the reactivity of these systems through the careful control of time<sup>14</sup>, reaction temperature<sup>15</sup> and the addition of additives<sup>16</sup>, there is still no general procedure that can guarantee selectivity for the desired product.

On the other hand, carbonyl reductive amination represents the most widely used alternative to *N*-alkylation for the preparation of aliphatic amines<sup>17,18</sup>. Its broad applicability lies in the efficacy of the condensation between an aldehyde or ketone with either a primary amine forming an imine, or an iminium ion in the case of a secondary amine. Subsequent reaction with a hydride source, such as  $\text{NaBH}_3\text{CN}$  or  $\text{NaBH}(\text{OAc})_3$ , leads to the alkylated amine product. While this approach is, today,

considered the benchmark reaction for amine synthesis, it is not without its shortcomings; poor reactivity in the case of sterically encumbered amines and ketones<sup>19</sup>, and over-reaction in the case of small, nucleophilic amines and simple aldehydes<sup>20</sup>. The undesirable use of super-stoichiometric hydride-type reagents, as well as the generation of toxic by-products, have led to the development of alternative reducing agents including catalytic hydrogenation<sup>21</sup>, formic acid<sup>22</sup>, silanes<sup>23</sup>, Hantzsch ester<sup>24</sup>, boranes<sup>25</sup> and transition metal hydrides<sup>26</sup>. Reductive amination is, however, not the sole reductive strategy for accessing aliphatic amines; both amides<sup>27</sup> and nitriles<sup>28</sup> are additionally suitable precursors for hydrogenation. Due to their lower electrophilicity compared to imines and iminium ions, more reactive aluminium hydrides<sup>29</sup> are typically employed in combination with Lewis or Brønsted acids<sup>30</sup>. Typically, these require challenging work-up procedures to cleave the boron or aluminium adducts, often requiring harsh acidic/basic conditions that can be incompatible with sensitive functionality. In recent decades, the tractability of imines has led to a surge in fields such as: organocatalysis, including the Aza-Morita-Baylis-Hilman<sup>31</sup>, Mannich<sup>32</sup> and cycloaddition reactions<sup>33</sup>; imine alkylation, including the use of Ellman's auxiliary<sup>34</sup>, Strecker<sup>35</sup> and Petasis reactions<sup>36</sup>; and Brønsted acid catalysis<sup>37</sup>.

Arguably, over the last fifty years transition metal catalysis has evolved to become one of the most important facets of modern synthetic organic chemistry<sup>38</sup>. With access to multiple oxidation states, bonding modes, and coordination environments, the novel chemical reactivity afforded to organotransition metal complexes has led to innovative solutions to long-standing synthetic challenges. For example, in 2009 Merck research laboratory disclosed a highly efficient asymmetric synthesis of sitagliptin (Januvia) **3**, used in the treatment of diabetes (Scheme 2)<sup>39</sup>. Using a [Rh(cod)Cl]<sub>2</sub> catalyst and chiral 'Bu-JOSIPHOS ligand, asymmetric hydrogenation of the intermediate enamide **1** to the corresponding primary amine could be accomplished in 98% yield and 95% e.e.. Deuterium labelling revealed that the *NH*-imine **2** was in fact the species that underwent hydrogenation. Generation of this intermediate via the addition of ammonia to the  $\beta$ -ketoamide could provide a viable alternative, potentially paving the way for new transition metal catalyzed asymmetric reductive amination technologies. Moreover, in 2010 Merck further disclosed a biocatalytic asymmetric reductive amination of pro-sitagliptin to sitagliptin using transaminase enzymes under physiological conditions (>99.95% e.e.)<sup>40</sup>, potentially heralding a new era in the art of amine synthesis<sup>41</sup>.



**Scheme 2** | Transition metal catalyzed asymmetric reductive amination for the synthesis of sitagliptin

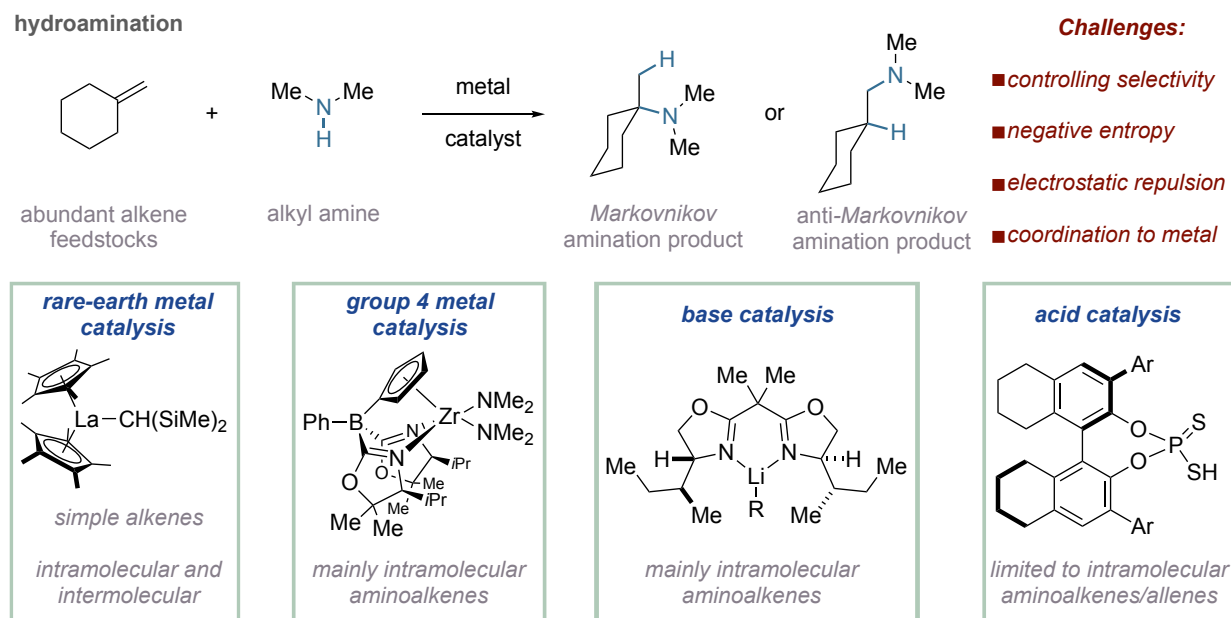
Nonetheless, the increasing demand for more complex amines in drug-discovery platforms has continued to drive the development of new and practical methods for the synthesis of these important molecules<sup>42</sup>. The aim of this introduction is to inform the reader about key areas of modern transition metal catalyzed approaches to alkylamine synthesis and functionalization: (a) hydroamination and hydroaminoalkylation; (b) transition-metal catalyzed C(*sp*<sup>3</sup>)-H functionalization; and (d) transition-metal mediated visible light photoredox catalysis – from important seminal work and historical context to state-of-the-art examples and applications.

## 1.2 Transition-metal catalyzed hydroamination and hydroaminoalkylation

The direct introduction of an amine moiety to unfunctionalized hydrocarbon feedstocks in the presence of a transition metal catalyst represents an ideal in amine synthesis. Along these lines, hydroamination - the reaction between a simple amine and an unactivated alkene, constitutes a particularly attractive and atom economical route for the synthesis of secondary and tertiary amines (Scheme 3). Despite the simplicity of this reaction, there are several factors that have impeded the development of a general strategy for the hydroamination of alkenes: (a) although generally exothermic, the negative entropy leads to a high reaction barrier; (b) electrostatic repulsion between the nitrogen lone pair and alkene  $\pi$ -system; (c) control of regioselectivity leading to intermolecular Markovnikov vs. *anti*-Markovnikov products; and (d) unfavourable competition between strongly Lewis basic amines and weakly co-ordinating alkenes.

In light of these numerous challenges, a variety of elegant catalytic manifolds have been developed utilizing rare-earth metal catalysts<sup>43,44</sup>, cationic group 4 (*d*<sup>0</sup>) metal complexes<sup>45–48</sup>, as well as chiral

Brønsted acid<sup>49,50</sup> and base catalysis<sup>51,52</sup>. These topics have been extensively reviewed elsewhere<sup>53</sup> and this chapter will focus on key developments in transition metal catalysed approaches towards hydroamination<sup>54</sup>.

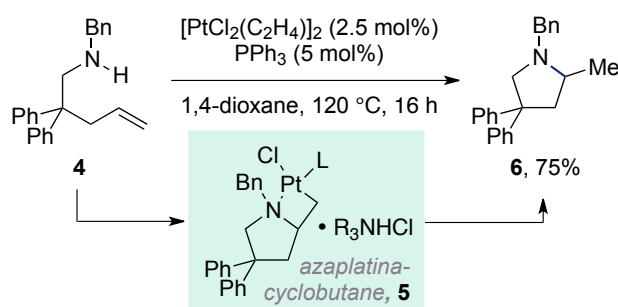


**Scheme 3** | Overview of hydroamination

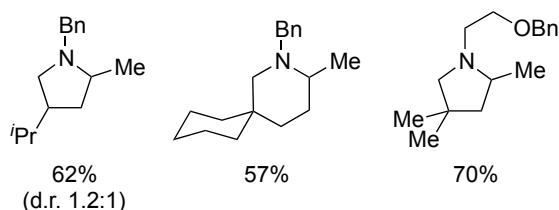
### 1.2.1 Intramolecular hydroamination

The intramolecular hydroamination of alkenes, where both the amine and alkene are tethered together in the same molecule, overcomes one of the principal challenges associated with hydroamination, namely competitive ligation between the strongly-coordinating amine and poorly-coordinating alkene. The use of late-transition metal catalysts, particularly Lewis acidic  $d^8$  and  $d^{10}$  metal complexes such as  $Rh^I$ ,  $Ir^I$ ,  $Pt^{II}$  and  $Au^I$ , gives rise to strong transition metal  $\pi$ -alkene complexes, which activate the alkene towards nucleophilic attack<sup>38</sup>. As early as 1975, Zambonelli reported the reaction of  $Na_2[PtCl_4]$  with 4-pentenylammonium chloride, affording 2-methylpyrrolidinium chloride after prolonged heating<sup>55</sup>. However, the first headway towards a general catalytic strategy was made by Widenhoefer in 2005 using Zeise's dimer and triphenylphosphine (Scheme 4)<sup>56</sup>. Under these conditions, a variety of  $\gamma$ - and  $\delta$ -amino alkenes **4** were found to be suitable substrates for the intramolecular Markovnikov hydroamination, delivering the corresponding 2-methylpyrrolidines **6** and piperidines in good yields. Recent mechanistic investigations have revealed the key hydroamination step occurs via the outer-sphere attack of the pendant amine to the  $Pt-(\pi\text{-alkene})$  complex and the turnover limiting intramolecular protonolysis of the azaplatinacyclobutane-ammonium ion adduct **5**<sup>57</sup>.

## Widenhoefer (2005)

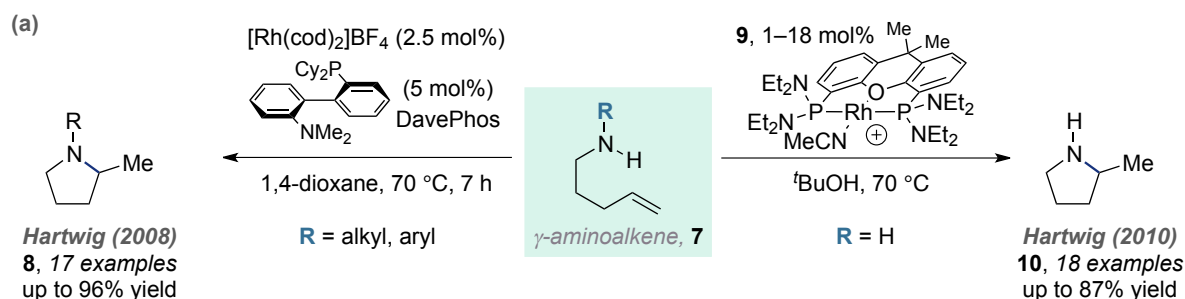


## representative examples

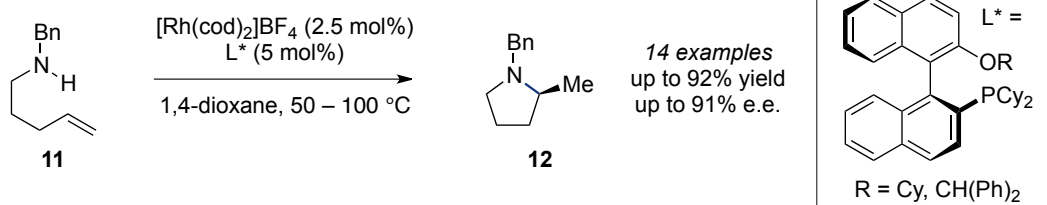


Scheme 4 | Intramolecular hydroamination of secondary alkylamines

In 2008, Hartwig detailed several reports of  $\text{Rh}^{\text{I}}$ -catalyzed intramolecular hydroamination of aliphatic primary and secondary  $\gamma$ -aminoalkenes **7**, underlining a new direction in the field (Scheme 5a)<sup>58</sup>. The use of DavePhos as a ligand for secondary amines was crucial in preventing oxidative amination, alkene isomerization and hydrogenation by-products, delivering the corresponding cyclic amines in excellent yields with good functional group tolerance **8**. Interestingly, mechanistic studies revealed that due to their stronger coordination with electrophilic metal centres, the rate-limiting step for  $\text{Rh}^{\text{I}}$ -catalyzed primary amine hydroamination was found to be attack of the amine to the alkene, whereas for secondary amines,  $\text{Rh}-\text{C}$  bond cleavage was shown to be rate-limiting. Accordingly, a more electrophilic cationic  $\text{Rh}$ -catalyst using a Xantphos-type ligand **9** gave superior results for intramolecular primary amine hydroamination **10**<sup>59</sup>.



## (b) Buchwald (2010)

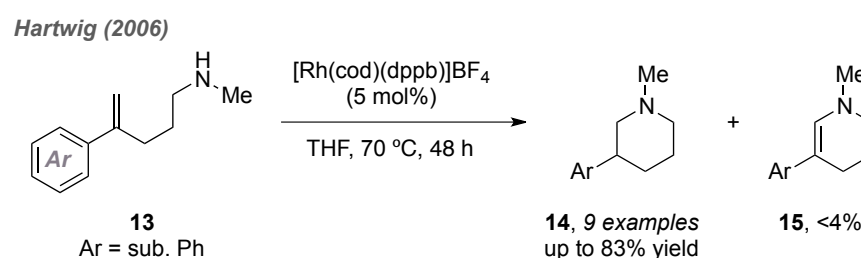


Scheme 5 | (a) Rh-catalyzed intramolecular hydroamination. (b) Asymmetric hydroamination

In 2010, Buchwald reported the first  $\text{Rh}$ -catalysed asymmetric intramolecular hydroamination of unactivated alkenes **11** using  $[\text{Rh}(\text{cod})_2]\text{BF}_4$  and Cy-MOP-type ligands (Scheme 5b)<sup>60</sup>. The scope was comprised of synthetically useful benzyl amines, which afforded the corresponding pyrrolidines

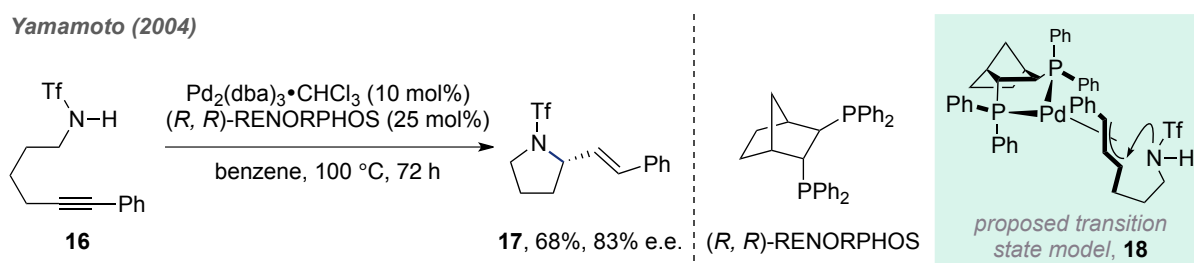
**12** in high yields and enantioselectivities (up to 91% e.e.). Despite later efforts by Michon<sup>61</sup> and Mikami<sup>62</sup> using Au<sup>I</sup> catalysts in conjunction with phosphoramidite ligands and chiral phosphoric acids, the procedure reported by Buchwald remains state-of-the-art in asymmetric intramolecular alkene hydroamination.

Despite the importance of piperidine motifs in pharmaceuticals and natural products<sup>63</sup>, efforts towards the intramolecular *anti*-Markovnikov hydroamidation of unactivated alkenes have remained limited due to competing oxidative amination **15**. Seminal work by Hartwig in 2006 described the Rh-catalyzed intramolecular *anti*-Markovnikov hydroamidation of vinyl arenes **13** using a dppb ligand, yielding 3-arylpiperidines **14** in good yields and excellent regioselectivities (Scheme 6)<sup>64</sup>.



**Scheme 6** | Anti-Markovnikov intramolecular hydroamination

In addition to the hydroamination of alkenes, significant progress has been made on other unsaturated functionalities including alkynes and allenes<sup>54</sup>. Although the hydroamination of alkynes traditionally generates enamines/imines, a particularly interesting report by Yamamoto in 2004 using Pd<sup>II</sup>-catalysis detailed the intramolecular asymmetric hydroamidation of alkynyl triflamides **16** to generate chiral pyrrolidines **17** and piperdines (up to 91% e.e.) (Scheme 7)<sup>65</sup>. The authors speculate that initial hydropalladation of the alkyne, followed by  $\beta$ -hydride elimination, generates an allene. Further hydropalladation affords a  $\pi$ -allylpalladium complex **18**, which, upon intramolecular enantiodetermining attack of the triflamide, generates the chiral amine product and the catalytic Pd-H species.

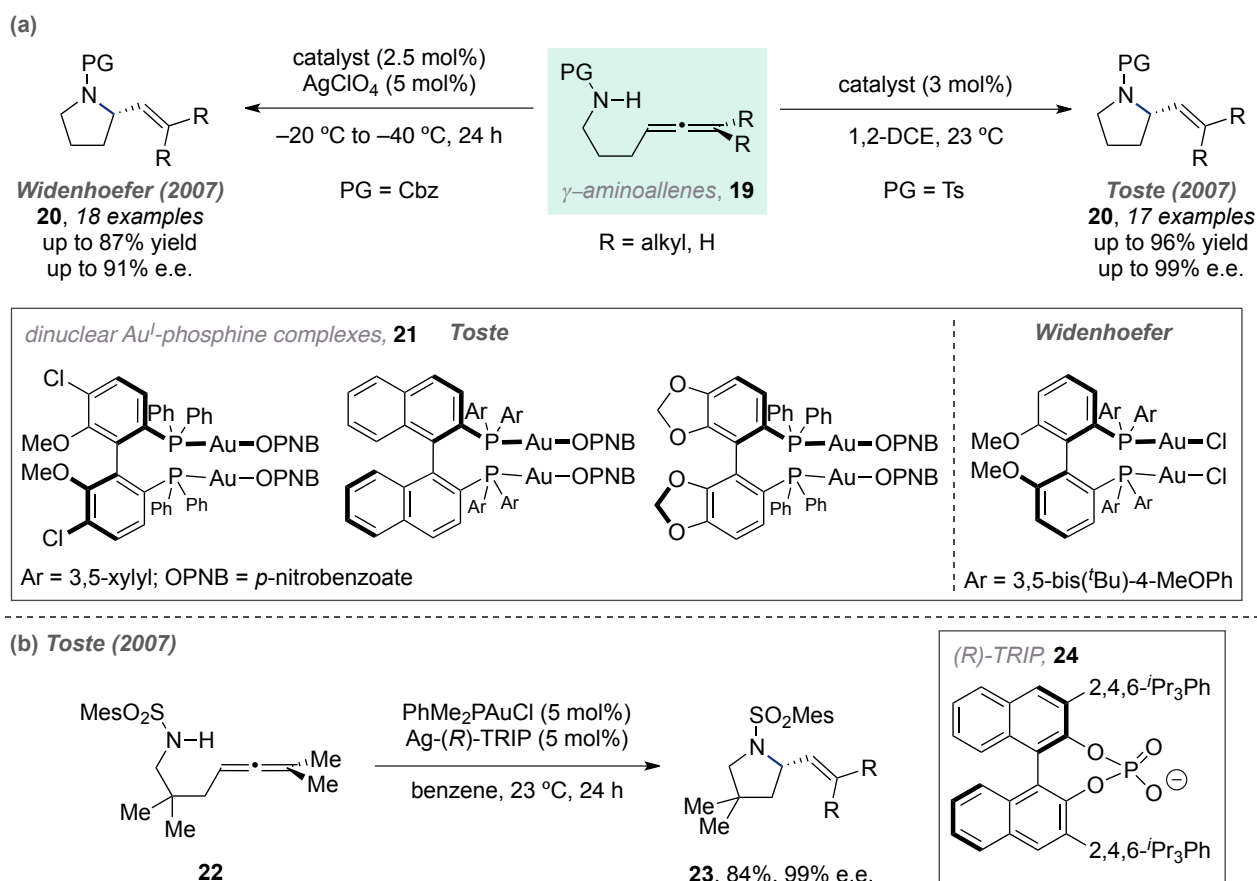


**Scheme 7** | Asymmetric intramolecular hydroamination of alkynes

The weaker C=C bond in allenes, compared with simple alkenes (~ 10 kcal/mol), offers a potential advantage for asymmetric transition-metal catalysis, whereby less forcing conditions are required<sup>66</sup>.



Due to their soft carbophilic character,  $\text{Au}^{\text{I}}$ -catalysts have garnered significant attention in this field<sup>67</sup>; however, due to the preferred linear geometry of  $\text{Au}^{\text{I}}$ -complexes, it was thought that the use of a chiral phosphine ligand would be too far removed from the reactive centre to induce chirality. Nevertheless, in 2007 Widenhoefer<sup>68</sup> and Toste<sup>69</sup> independently reported that chiral dinuclear  $\text{Au}^{\text{I}}$ -phosphine complexes **21** could promote the intramolecular hydroamidation of  $\gamma$ -aminoallenes **19**, forming vinylpyrrolidines **20**, in good yields and high enantioselectivities (up to 99% e.e.) (Scheme 8a). Interestingly, a significant counterion effect was observed, in which the larger *para*-nitrobenzoate ligand was found to profoundly increase the relay of chiral information. In the same vein, Toste subsequently published a seminal report on the cationic  $\text{Au}^{\text{I}}$  chiral ion-pair mediated asymmetric hydroamidation of allenes **22** (Scheme 8b)<sup>70</sup>. Therein, the authors reported that by using a chiral phosphate based counterion **24** instead of a chiral phosphine ligand, significantly enhanced enantioselectivities could be obtained for vinylpyrrolidines **23** that had performed modestly under previous conditions.

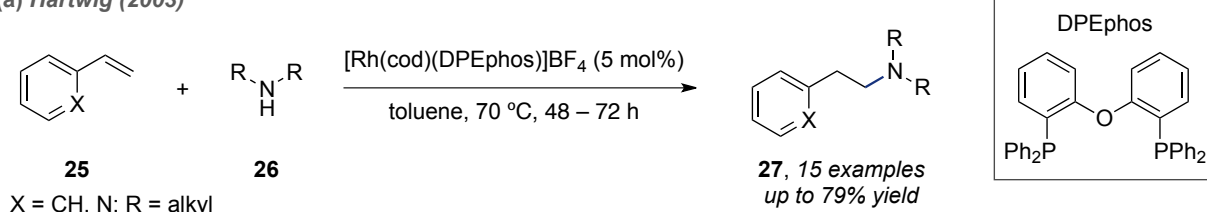


**Scheme 8** | (a) Asymmetric intramolecular hydroamination of allenes. (b) Chiral counterion based hydroamination

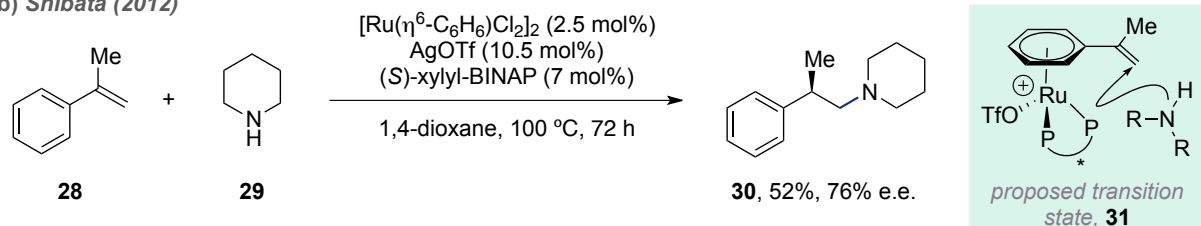
## 1.2.2 Intermolecular hydroamination

It wasn't until the turn of the 21<sup>st</sup> century that the first general procedures for transition metal-catalyzed intermolecular alkene hydroamination were reported by Beller<sup>71</sup>. Due in part to their ability to pre-coordinate to transition metal catalysts, these early reports centred around the use of vinyl arenes as alkene coupling partners. In contrast to intramolecular hydroamination, Rh<sup>I</sup>-catalyzed intermolecular hydroamination occurred with notable *anti*-Markovnikov selectivity. However, these reactions gave low yields of the desired hydroamination products, instead forming oxidative amination products via deleterious  $\beta$ -hydride elimination of the intermediate Rh-alkyl species<sup>72</sup>. Despite these challenges, in 2003 Hartwig outlined a general strategy for the Rh/DPEphos-catalyzed hydroamination of vinyl (hetero)arenes **25** with dialkylamines **26**, furnishing phenethylamine products **27** in good yields (Scheme 9a)<sup>73</sup>. The following year, Hartwig further detailed the *anti*-Markovnikov hydroamination of vinyl arenes utilizing a combination of ( $\eta^6$ -styrene)-Ru catalyst and Brønsted acid – the use of which is thought to contribute by both protonating the amine to allow preferential coordination of the alkene, as well as aid in the protolytic cleavage of the metal-carbon bond<sup>74</sup>. Mechanistically distinct, experimental evidence strongly indicates that the reaction proceeds via nucleophilic attack of an amine to the bound ( $\eta^6$ -styrene)-Ru complex **31**, followed by deligation of the product and coordination of a new vinyl arene<sup>75</sup>. In 2012, Shibata reported the first enantioselective *anti*-Markovnikov hydroamination of  $\alpha$ -methylstyrenes **28** using secondary aliphatic amines **29** (Scheme 9b)<sup>76</sup>. By employing (*S*)-xylylBINAP as a ligand in combination with an ( $\eta^6$ -benzene)-Ru catalyst,  $\beta$ -methylphenethylamines **30** up to 76% e.e. could be achieved, albeit with modest yields.

(a) Hartwig (2003)

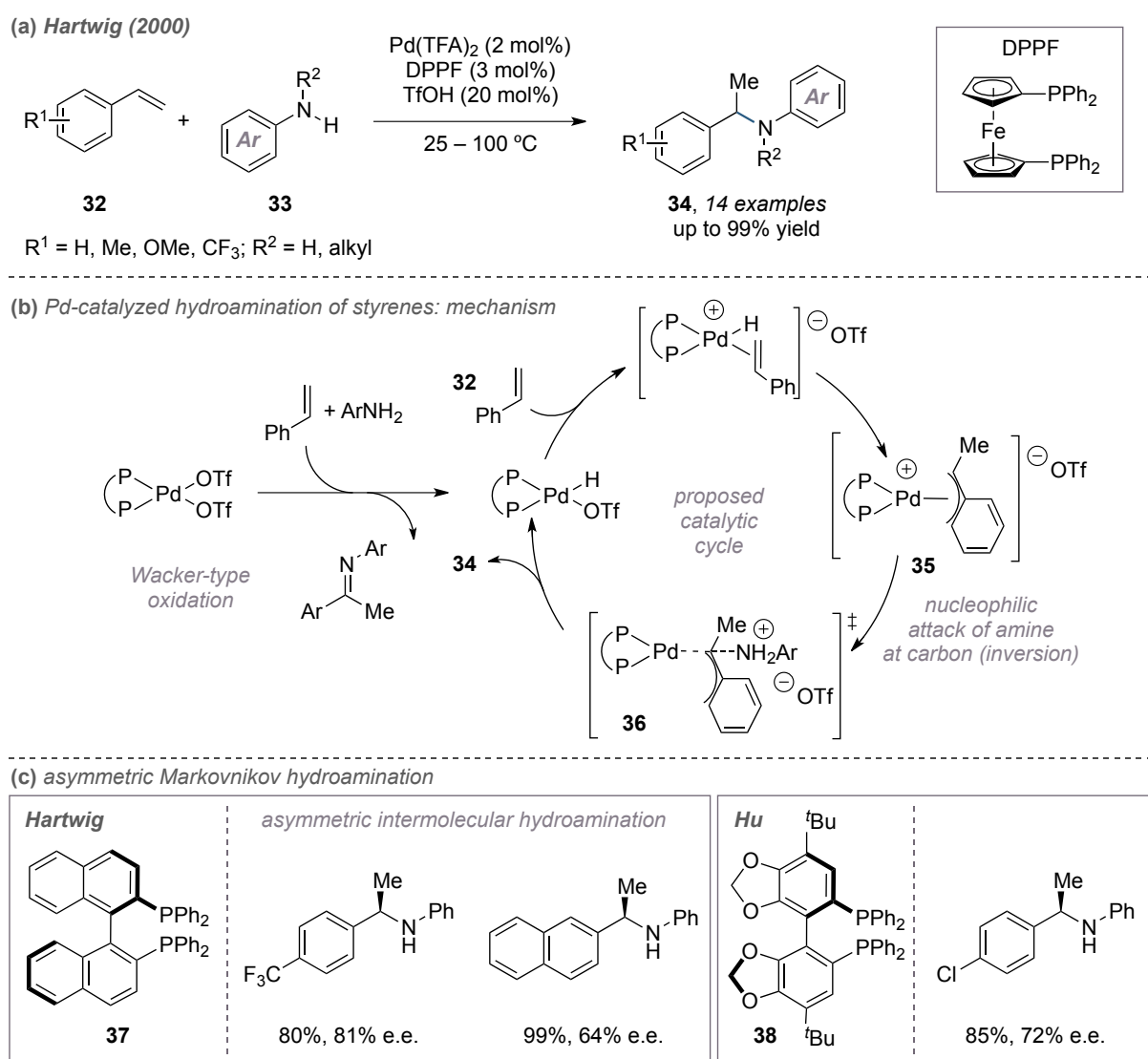


(b) Shibata (2012)



Scheme 9 | (a) Intermolecular hydroamination of vinyl arenes. (b) Asymmetric intermolecular hydroamination

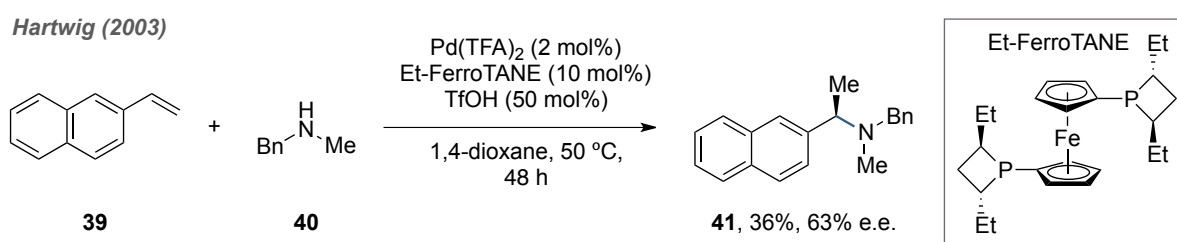
In 2000, Hartwig described the Pd-catalyzed intermolecular hydroamination of vinyl arenes **32** with anilines **33** in good yields, using a combination of Pd(OTf)<sub>2</sub>, DPPF and TfOH (Scheme 10a)<sup>77</sup>. In contrast to Rh-catalyzed processes, the Pd-catalyzed transformation exclusively afforded the Markovnikov products **34**. Mechanistic studies revealed that insertion of the alkene into the Pd–H bond occurred first, giving rise to a  $\eta^3$ -benzyl species **35**, followed by external nucleophilic attack of the amine **36** (Scheme 10b)<sup>78</sup>. Preliminary studies by Hartwig using chiral BINAP ligands<sup>77</sup>, followed later by Hii<sup>79</sup> and Hu<sup>80</sup>, gave rise to good yields and enantioselectivities (up to 81% e.e.) (Scheme 10c).



**Scheme 10** | (a) Intermolecular Markovnikov hydroamination. (b) Proposed mechanism. (c) Asymmetric hydroamination

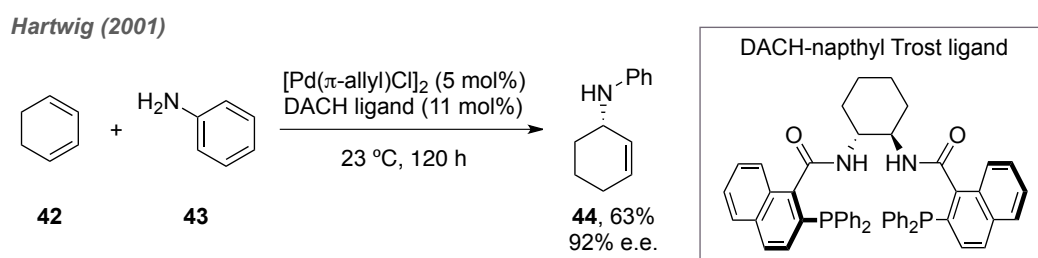
While significant advancements had been accomplished using aryl-derived amines, the use of simple aliphatic amines proved more challenging. It was reasoned that the greater basicity of alkylamines resulted in competitive deprotonation of the intermediate  $\eta^3$ -benzyl species, liberating the starting alkene. Nevertheless, in 2003 Hartwig described the intermolecular hydroamination of vinyl arenes

with aliphatic secondary amines in modest to good yield via judicious control of solvent and catalyst/ligand loadings<sup>81</sup>. Moreover, the reaction between *N*-methylbenzylamine **40** and 2-vinylnaphthalene **39** was rendered asymmetric using a chiral Et-FerroTANE ligand, furnishing  $\alpha$ -methylbenzylamine **41**, albeit in low yield (36%) and moderate enantioselectivity (63% e.e.) (Scheme 11). Nevertheless, this remains the only example of transition metal catalyzed intermolecular asymmetric hydroamination of alkenes with alkylamines.



**Scheme 11** | Asymmetric intermolecular hydroamination using alkylamines

Compared to alkenes, the intermolecular hydroamination of 1,3-dienes to generate allylic amines has itself received comparatively little attention due to difficulties in controlling regioselectivity. Nevertheless, the early 2000's saw a major development in both the Ni- and Pd-catalyzed hydroamination of cyclic 1,3-dienes **42**<sup>82–85</sup>. In 2001, Hartwig described an enantioselective hydroamination using a combination of  $[\text{Pd}(\pi\text{-allyl})\text{Cl}]_2$  and DACH-naphthyl Trost ligand, although long reaction times are required to ensure good conversion (Scheme 12)<sup>86</sup>. Both electron-rich and electron-poor anilines **43** underwent smooth hydroamination affording the allylic amine products in high yields and enantioselectivities (up to 95% e.e.).

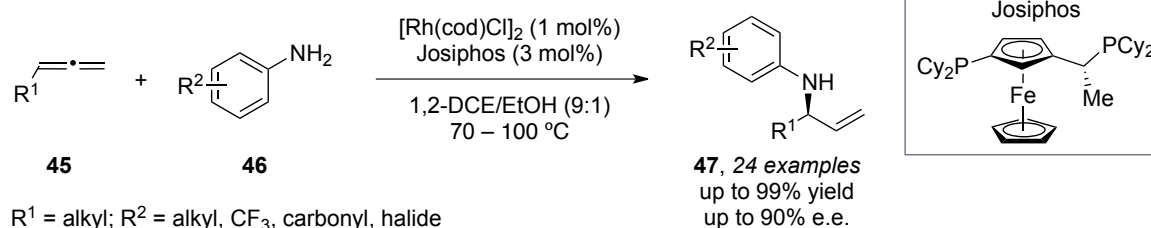


**Scheme 12** | Asymmetric hydroamination of 1,3-dienes

Although the intermolecular hydroamination of allenes has been known since 1976<sup>87</sup>, Yamamoto reported the first general strategy in 1997 using Pd-catalysis<sup>88</sup>. Despite intensive efforts by Schmidt, bespoke  $\text{Pd}^{\text{II}}$ -catalysts are required in order to achieve high selectivities<sup>89–92</sup>. Although Yamamoto<sup>93,94</sup> and Widenhoefer<sup>95,96</sup> have accomplished significant work using Au-catalysis, a recent elegant report by Breit described the first asymmetric intermolecular hydroamination of allenes **45** with anilines **46** using a  $\text{Rh}^{\text{I}}$ /Josiphos-catalyst in excellent yields and high enantioselectivities (up to 90% e.e.) (Scheme 13)<sup>97</sup>. Mechanistic studies suggest that oxidative addition of the aniline affords a  $\text{Rh}^{\text{III}}\text{-H}$ , which following hydrometallation of the allene to form the  $\pi$ -allyl-Rh complex, undergoes

reductive elimination to afford the allylic amine **47**. The catalyst system was further extended to encompass imidazole<sup>98</sup>, and more recently, 2-pyridones in similarly high enantioselectivities<sup>99</sup>.

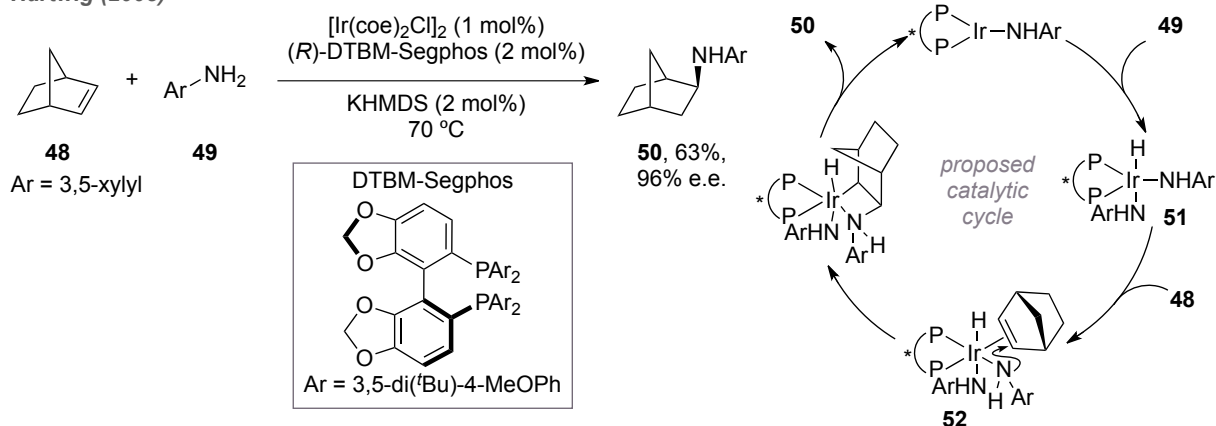
Breit (2012)



**Scheme 13** | Asymmetric hydroamination of allenes

Unlike activated alkenes such as vinyl arenes, allenes and 1,3-dienes, that benefit from pre-coordination to the metal catalyst, aliphatic alkenes are far less disposed towards hydroamination. As such, reports of intermolecular hydroamination of aliphatic alkenes are rare and typically require large excesses of alkene or strained systems. Inspired by the earlier efforts of Milstein<sup>100</sup>, Togni reported the first enantioselective variation of the reaction in 1997 using an Ir-BINAP catalyst in combination with a fluoride source<sup>101</sup>. Despite the high enantioselectivities achieved with this system, the poor turn-over limited its general applicability. Later, Hartwig reported an improved asymmetric hydroamination of bicyclic alkenes **48** using anilines **49** (Scheme 14)<sup>102</sup>. It is proposed that the combination of  $[\text{Ir}(\text{coe})_2\text{Cl}]_2$  catalyst and DTBM-Segphos ligand alongside catalytic KHMDS, replacing fluoride as a base, gives rise to the bis(amido)-Ir<sup>III</sup> species **51**, which upon insertion of the alkene **52**, furnishes the corresponding amine **50** upon reductive elimination in high yields and excellent enantioselectivities (up to 99% e.e.).

Hartwig (2008)

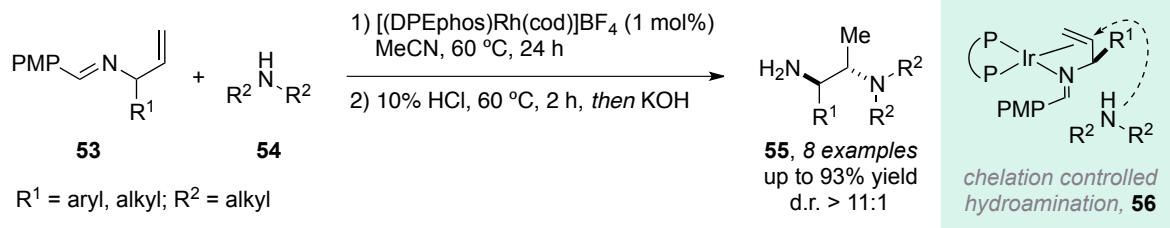


**Scheme 14** | Asymmetric Ir-catalyzed hydroamination of unactivated alkenes

Recently, an elegant strategy reported by Hull incorporated a Lewis-basic imine pendant to the alkene **53** in order to direct the Rh-catalyzed hydroamination event **56** (Scheme 15)<sup>103</sup>. Advantageously, the additional chelation served not only to promote hydroamination, using

dialkylamines **54**, but also prevented competing  $\beta$ -hydride elimination from the Rh-alkyl intermediate. The reaction demonstrated good substrate scope, affording a range of diamines after hydrolysis in good yields and excellent diastereoselectivities.

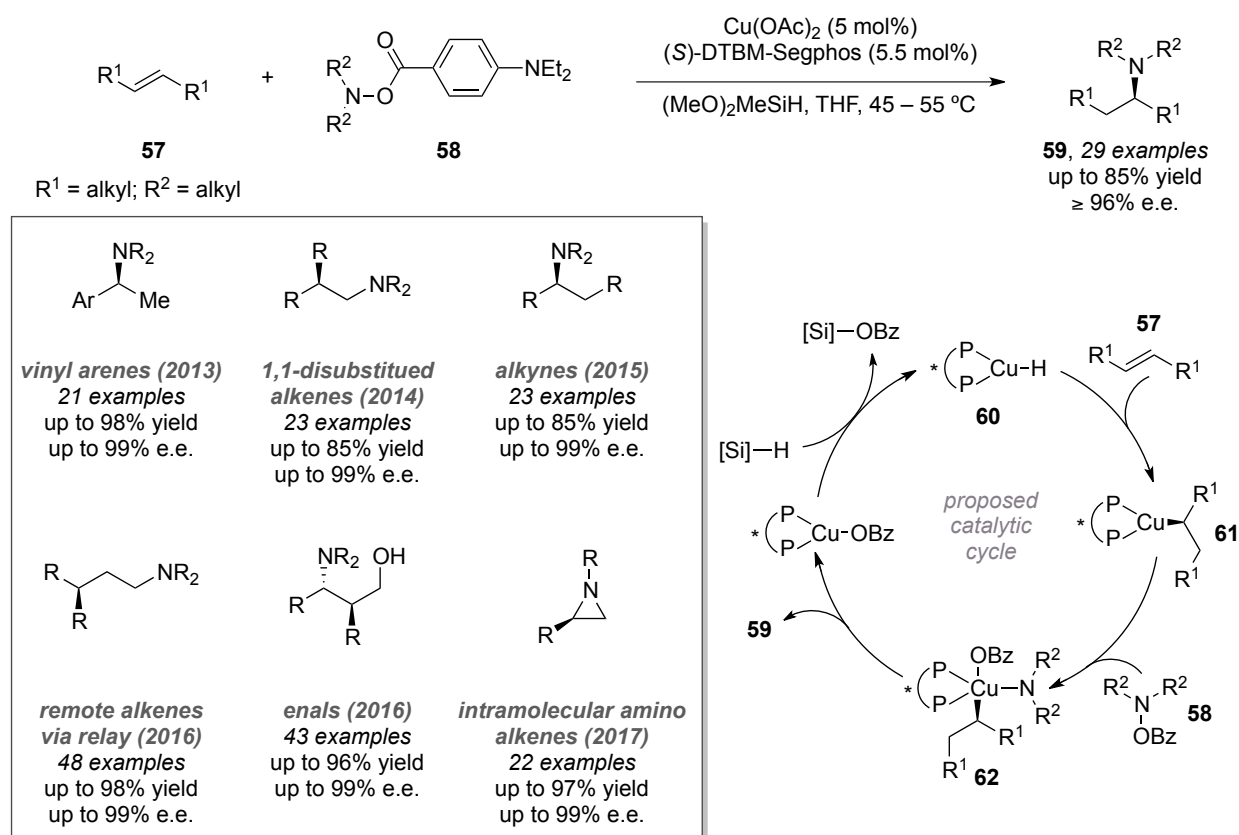
Hull (2014)



**Scheme 15** | Chelation assisted intermolecular hydroamination

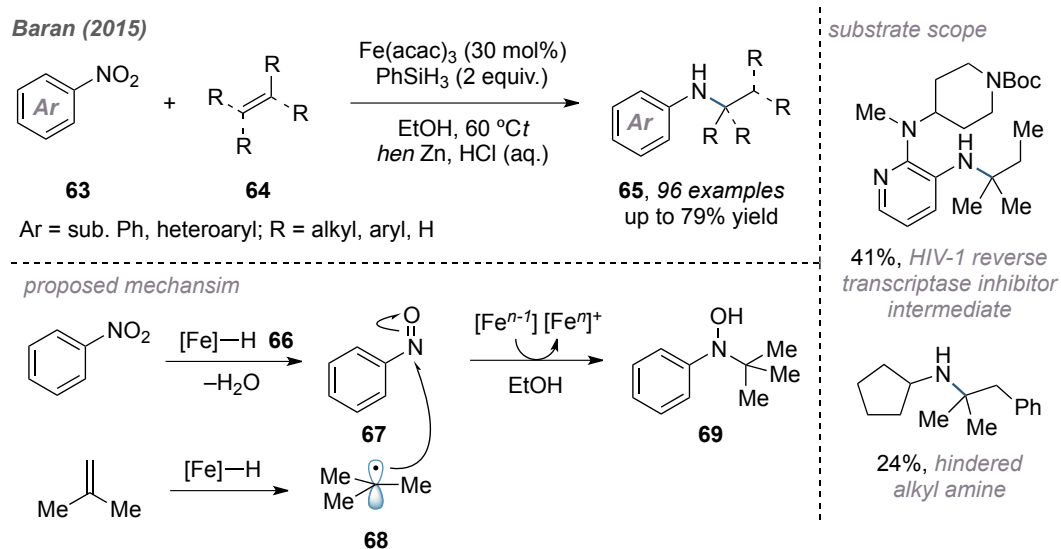
In 2013, both Miura<sup>104</sup> and Buchwald<sup>105</sup> detailed the Cu-catalyzed intermolecular asymmetric hydroamination of alkenes **57** using *O*-benzoylhydroxylamines **58** and Ph-BPE and DTBM-Segphos ligands respectively. The authors postulated that the enantiodetermining step is insertion of the alkene into a Cu–H species **60**. The resulting Cu-alkyl species **61** undergoes oxidative addition with the *O*-benzoylhydroxylamine to generate a Cu<sup>III</sup>-intermediate **62**, which in combination with an external silane, undergoes reductive elimination of the product **59**, regenerating the Cu–H catalyst.

Buchwald (2015) – Internal alkenes



**Scheme 16** | Asymmetric Cu-catalyzed hydroamination

Buchwald has since reported numerous hydroamination transformations delivering both tertiary and secondary amines<sup>106</sup>, using an array of substituted terminal<sup>107,108</sup> and internal alkenes<sup>109</sup>, alkynes<sup>110</sup>, enals and enones<sup>111</sup>, remote alkenes (via a relay process)<sup>112</sup>, as well as internal hydroamination to produce enantiopure azetidines<sup>113</sup> (Scheme 16). The scope, yield and enantioselectivities (up to 99% e.e.) have rendered this procedure the current state-of-the-art in olefin hydroamination.



**Scheme 17** | Fe-catalyzed hydroamination of nitroarenes

In 2015, Baran described a novel alkene hydroamination utilizing nitroarenes as the amine source (Scheme 17)<sup>114</sup>. Using a combination of  $\text{Fe}(\text{acac})_3$  catalyst and phenylsilane, the authors propose that a transient  $\text{Fe}-\text{H}$  species **66** acts to deliver both a H-radical to the nitroarene **63**, furnishing the nitrosoarene **67** with loss of water, as well as convert the alkene **64** to the corresponding alkyl radical **68**. Although the precise mechanism is unclear, it is postulated that alkyl radical addition to the nitroso group results in a hydroxylamine **69** that is subsequently reduced to the amine product **65**, either as part of the catalytic cycle or at the end of the reaction ( $\text{Zn}/\text{HCl}$ ). Due to the radical nature of the reaction, hindered amines were readily accessed from the stable 3° alkyl radicals; challenging products to access via traditional hydroamination techniques. Moreover, the reaction exhibited remarkable functional group tolerance including unprotected alcohols and amines. Encouragingly, nitroalkanes were found to react under the reaction conditions, affording difficult to access  $\alpha$ -tertiary amine products, albeit in low yields.

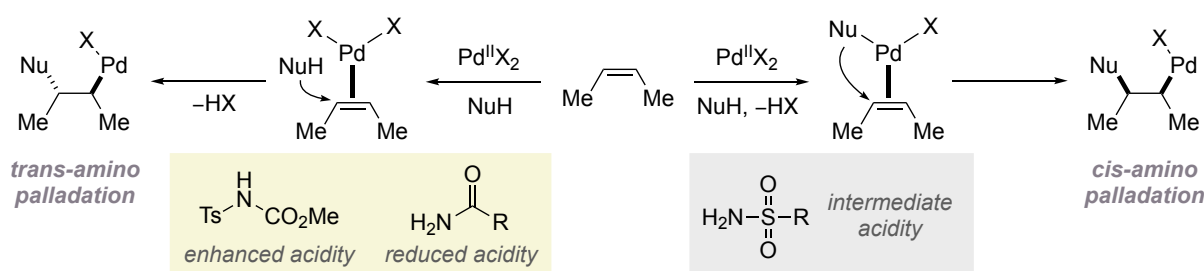
### 1.2.3 Alkene aminofunctionalization

Broadly speaking, hydroamination constitutes a subset of the more general class of alkene functionalization reaction, whereby an alternative group instead of hydrogen is installed on the

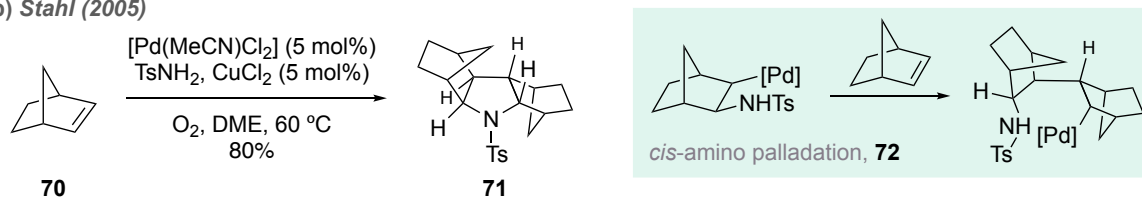


opposing alkene terminus. Ground-breaking work in the late 1950's saw the development of the Wacker oxidation – the Pd-catalyzed aerobic oxidative coupling of water and ethylene to produce acetaldehyde<sup>115,116</sup>. Soon after its discovery, a number of groups reported that Pd<sup>II</sup> could facilitate the addition of several nucleophiles, including amines<sup>117,118</sup>, to simple alkenes<sup>119</sup>. Interestingly, the nucleopalladation of alkenes often results in the formation of new stereogenic centres; however, controlling the stereochemical outcome can be challenging. A mechanistic basis for nucleopalladation occurs via two possible pathways: (a) *trans*-nucleopalladation where the nucleophile attacks on the opposite face to a Pd-bound alkene, and (b) *cis*-nucleopalladation where attack of the alkene occurs intramolecularly from a Pd-bound nucleophile (Scheme 18a).

(a) mechanistic basis for nucleopalladation



(b) Stahl (2005)



**Scheme 18** | (a) Mechanistic pathways for nucleopalladation. (b) Aminopalladation of norbornene

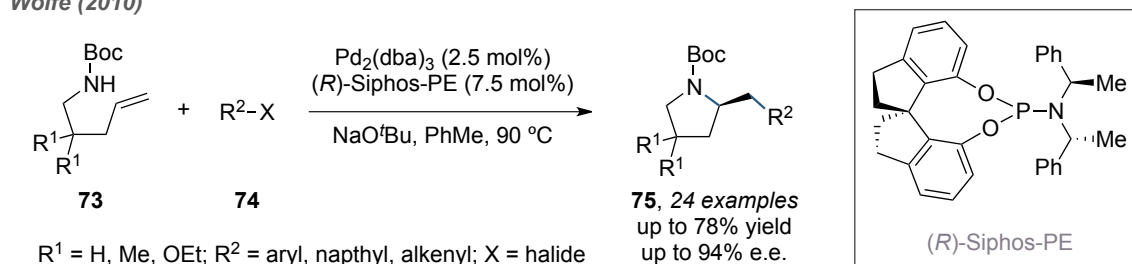
Mechanistic studies by Stahl have shown that the Pd-catalyzed reaction between norbornene **70** and TsNH<sub>2</sub> results in a C<sub>2</sub>-symmetric pyrrolidine **71**, resulting from *cis*-specific insertion of an alkene into a Pd–N bond **72** (Scheme 18b)<sup>120</sup>. Collective experimental results over the last four decades have revealed a subtle interplay between substrate nucleophilicity and acidity<sup>121</sup>; the energy barriers between the two competing pathways are very similar, and in some cases, can operate in parallel. Consequently, this has hampered the development of enantioselective processes. Moreover, chiral phosphine ligands are often incompatible with strong oxidants and their σ-donating ability can offset the electrophilicity of the Pd<sup>II</sup> catalyst. Despite this, the versatility of Pd in undergoing oxidative addition and carbonylation has resulted in the development of numerous synthetically valuable transformations, which have been the subject of several reviews<sup>119,122</sup>.

In 2004 Wolfe reported the Pd-catalyzed intramolecular aminoarylation of alkenes **73** to generate pyrrolidines **75** in good yields and excellent regioselectivities (up to 88% yield) (Scheme 19)<sup>123</sup>. The authors propose that following oxidative addition of the aryl bromide **74**, coordination of the amine

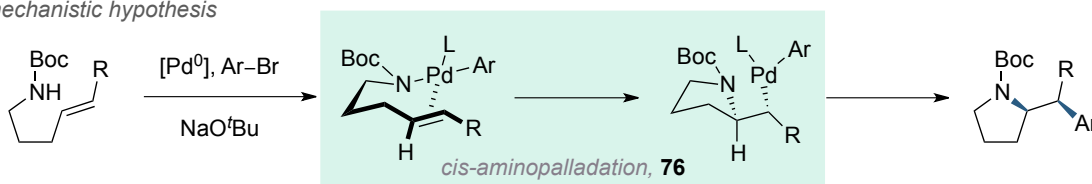


and base-induced dehydrobromination furnishes an intermediate Pd–amido species. Insertion of the alkene into the Pd–N bond generates a Pd–alkyl species **76**, which affords the cyclized amine product upon reductive elimination. The observation of *N*-arylated and regioisomeric products lends credence to the existence of a Pd–N bound intermediate; the regioisomers formed via a  $\beta$ -hydride/alkene re-insertion/reductive elimination pathway<sup>124</sup>. Given that aminoarylation occurred exclusively via a *cis*-aminopalladation pathway, an enantioselective aminoarylation was subsequently reported in 2010 employing catalytic Pd<sub>2</sub>(dba)<sub>3</sub> and (*R*)-Siphos-PE as a chiral ligand alongside NaO<sup>t</sup>Bu as a base<sup>125</sup>.

Wolfe (2010)

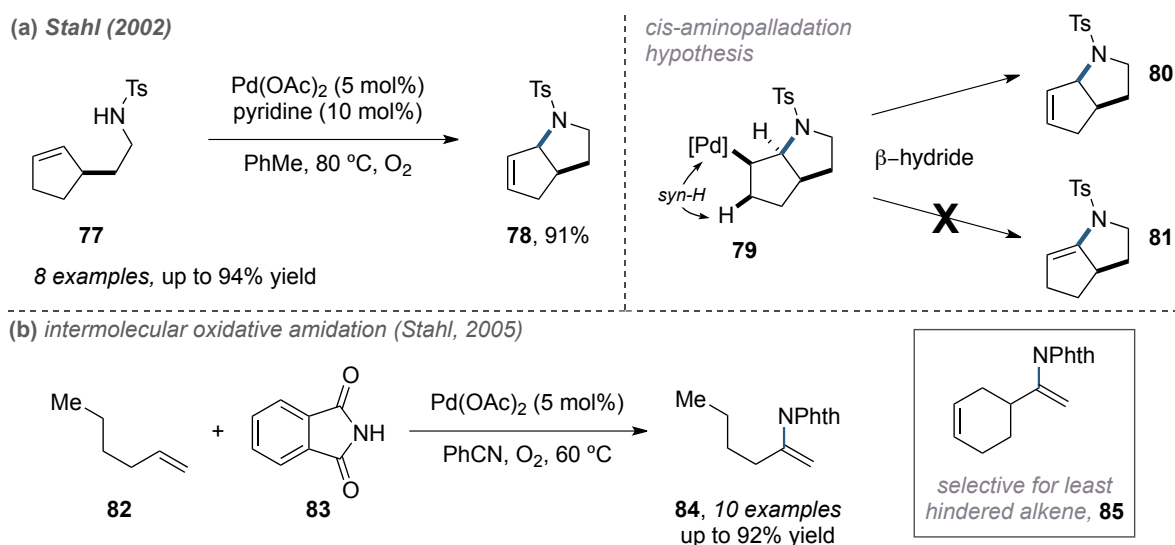


mechanistic hypothesis



Scheme 19 | Intramolecular *cis*-selective aminoarylation of alkenes

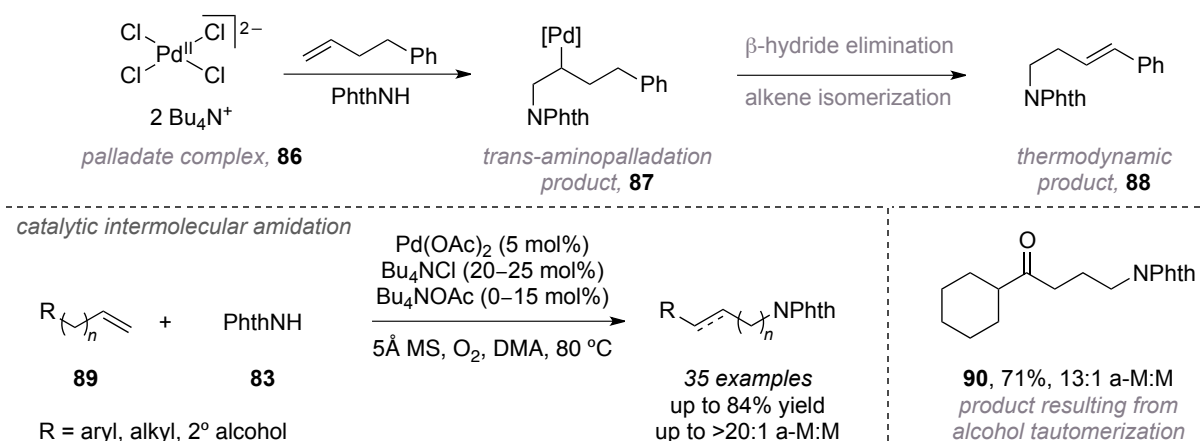
In contrast to aminoarylation whereby aminopalladation occurs from an electron-rich Pd<sup>II</sup>-aryl species, Wacker-type oxidative amination occurs via aminopalladation/ $\beta$ -hydride elimination from an electrophilic Pd<sup>II</sup>-catalyst. Early studies by Andersson<sup>126</sup>, Larock<sup>127</sup> and Stahl<sup>128</sup> revealed that alkenyl tosylamides **77** could undergo Pd<sup>II</sup>-catalyzed intramolecular cyclization to generate unsaturated heterocycles **78** in good yields (Scheme 20a). Employing a combination of Pd(OAc)<sub>2</sub>/O<sub>2</sub>/pyridine as an efficient catalyst system, without the need for a co-oxidant, formation of the allylic amine product **80** in preference to the imine/enamine **81** was attributed to selective *cis*-aminopalladation **79**. In 2005, Stahl extended the scope of the reaction to include the intermolecular Pd(OAc)<sub>2</sub>-catalyzed Markovnikov oxidative amination of aliphatic alkenes **82** with phthalimides **83** and sulfonamides, affording protected enamines **84**, in good yields and selectivities (up to 92%), albeit with large excesses of alkene (Scheme 20b)<sup>120</sup>. The reaction showed impressive selectivity for the amination of terminal over internal alkenes **85**; however, the substrate scope was limited to simple aliphatic alkene systems.



**Scheme 20** | (a) Intramolecular oxidative aminopalladation. (b) Intermolecular oxidative amidation

In 2018, Hull described the first highly selective Pd-catalyzed *anti*-Markovnikov oxidative amination of aliphatic alkenes **89**, with phthalimide **83**, in moderate to good yields and good selectivities (up to 84% yield, up to >20:1 a-M:M) (Scheme 21)<sup>129</sup>. Using a palladate catalyst **86** saturated with excess halide, *trans*-nucleopalladation occurred selectively at the least hindered alkene terminus **87**. Additionally, olefin isomerization occurred either into conjugation with an aromatic **88** or heteroatom **90** (leading to tautomerization), acting as an overall thermodynamic driving force for the reaction.

*anti*-Markovnikov oxidative amidation strategy (Hull, 2018)



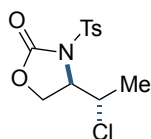
**Scheme 21** | Anti-Markovnikov intermolecular oxidative amidation

Over the last decade, several reports of intramolecular Pd-catalyzed amino-difunctionalization have been described. Recent examples include aminoacetoxylation<sup>130</sup>, aminohalogenation<sup>131</sup>, aminofluorination<sup>132</sup> and diamination<sup>133</sup> (Scheme 22a). Despite the high levels of diastereoselectivity, either *cis* or *trans*, attempts to translate this important reactivity into an enantioselective transformation has been met with limited success. Amongst the most successful

protocols reported, Yang recently described the Pd-catalyzed intramolecular aminovinylolation of *N*-acryloyl anilides **91**, generating pyrroloindolones **92**, in good yields and high enantioselectivities (up to 82% yield, up to 98% e.e.) using a *tert*-Bu-quinoxaline ligand (Scheme 22b)<sup>134</sup>.

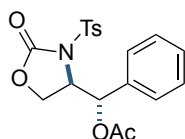
(a) aminodifunctionalization reactions

aminohalogenation



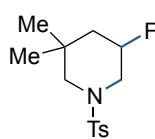
Liu (2004)  
8 examples  
up to 97% yield

aminoacetoxylation



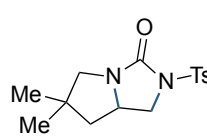
Sorensen (2005)  
9 examples  
up to 92% yield

aminofluorination



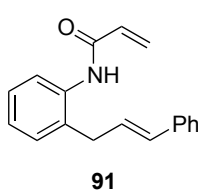
Liu (2009)  
12 examples  
up to 89% yield

diamination



Muñiz (2005)  
9 examples  
up to 95% yield

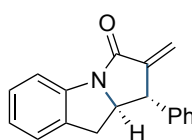
(b) asymmetric aminovinylolation (Yang, 2009)



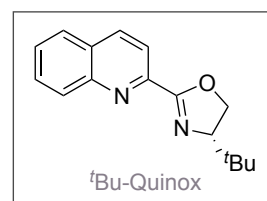
**91**

$\text{Pd}(\text{MeCN})_2\text{Cl}_2$  (10 mol%)  
*t*Bu-Quinox (40 mol%)

$\text{AgOTf}$  (20 mol%), 3 Å MS  
 $\text{O}_2$ , PhMe, 75 °C



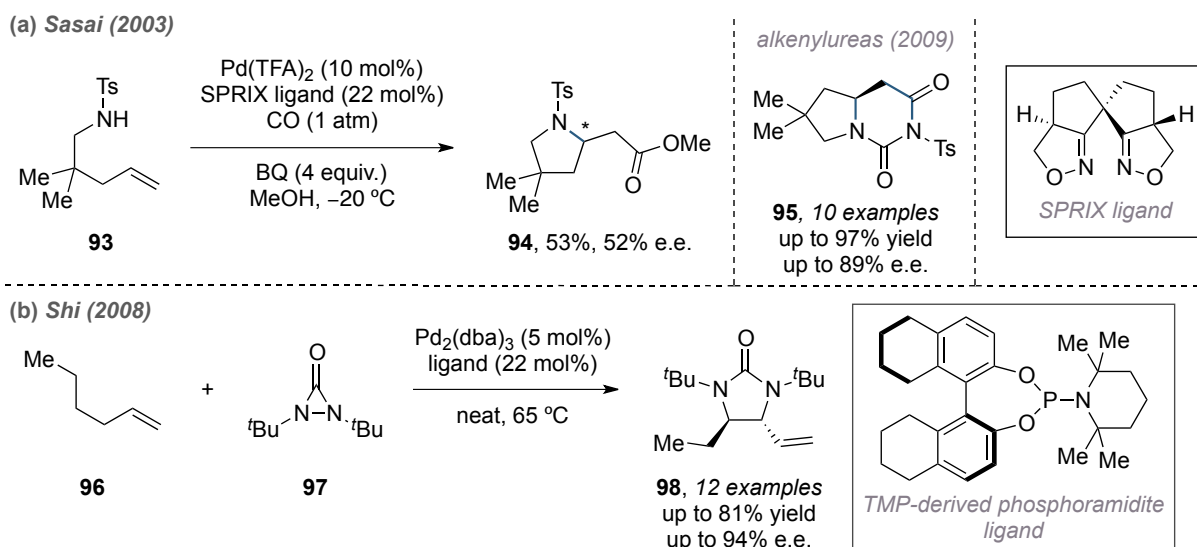
**92**, 11 examples  
up to 82% yield  
up to 98% e.e.



*t*Bu-Quinox

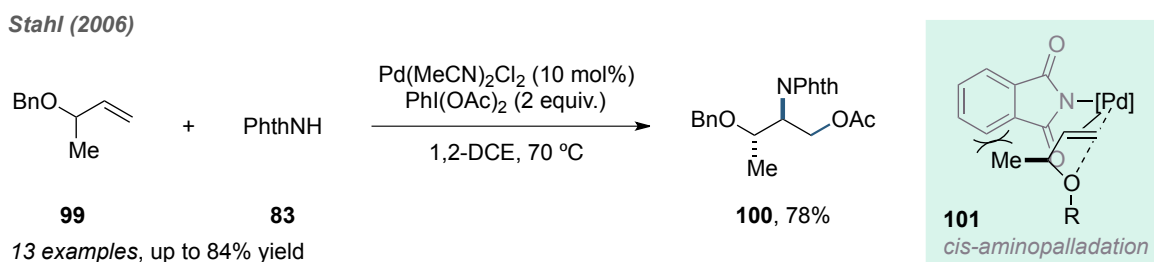
**Scheme 22** | (a) Overview of Pd-catalyzed amino-difunctionalization. (b) Asymmetric intramolecular aminovinylolation

Inspired by the early work by Tamaru<sup>135</sup>, Sasai described a procedure for the Pd-catalyzed aminocarbonylation of  $\gamma$ -alkenyl tosylamides **93** in good yields (up to 96%) (Scheme 23a)<sup>136</sup>. The authors propose that following intramolecular attack of the sulfonamide to the activated alkene, the resulting Pd-alkyl species undergoes CO insertion and methanolysis to afford the  $\beta$ -homoproline product **94**. Oxidation of the  $\text{Pd}^0$ -species using benzoquinone regenerates the active  $\text{Pd}^{\text{II}}$ -catalyst. Moreover, using a SPRIX ligand that is stable under oxidative conditions, moderate enantioselectivities could be achieved (up to 65% e.e.). In 2009, the scope was expanded to include the asymmetric aminocarbonylation of alkenylureas, forming pyrrolopyrimidones **95**, with improved enantioselectivities (up to 89% e.e.)<sup>137</sup>. In 2008, Shi described the  $\text{Pd}^0$ -catalyzed oxidative diamination of terminal alkenes **96** using di-*tert*-butylaziridinone **97** as both the oxidant and nitrogen nucleophile in good yields (up to 81% yield) (Scheme 23b)<sup>138</sup>. Furthermore, using a TMP-derived phosphoramidite ligand, the corresponding substituted imidazolidones **98** could be accessed in high enantioselectivities (up to 94% e.e.).



**Scheme 23** | (a) Intramolecular aminocarbonylation. (b) Asymmetric deamination of terminal alkenes

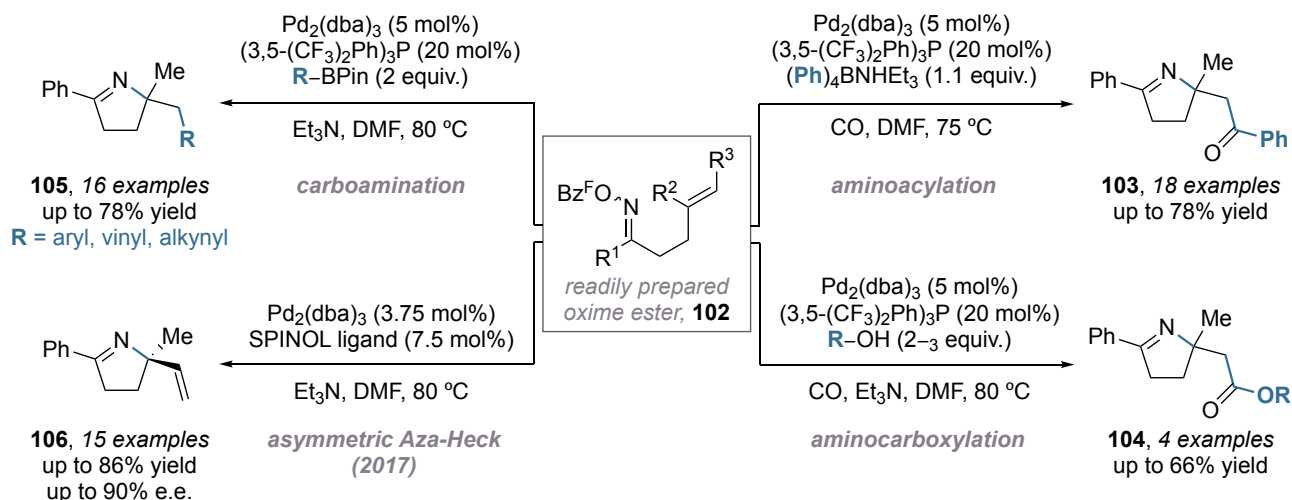
Despite notable work by Sanford on the intermolecular amination/cyclization of alkenyl alcohols<sup>139</sup>, a more general strategy for intermolecular amino-difunctionalization has been reported by Stahl<sup>140</sup>. Using a  $\text{Pd}(\text{OAc})_2$  catalyst and  $\text{PhI}(\text{OAc})_2$  oxidant, intermolecular Markovnikov aminoacetoxylation of terminal alkenes **99** using phthalimide **83** could be achieved in good yields and excellent regio- and *syn*-diastereoselectivities (up to 84% yield) (Scheme 24). The authors propose that high *syn*-selectivity results from *cis*-aminopalladation **101**. Further mechanistic studies revealed that aminoacetoxylation occurs via *cis*-aminopalladation of the alkenes followed by oxidation to  $\text{Pd}^{\text{IV}}$  and  $\text{S}_{\text{N}}2$  attack of an acetate to the  $\text{Pd}$ -alkyl bond, furnishing the protected aminoalcohol products **100**.



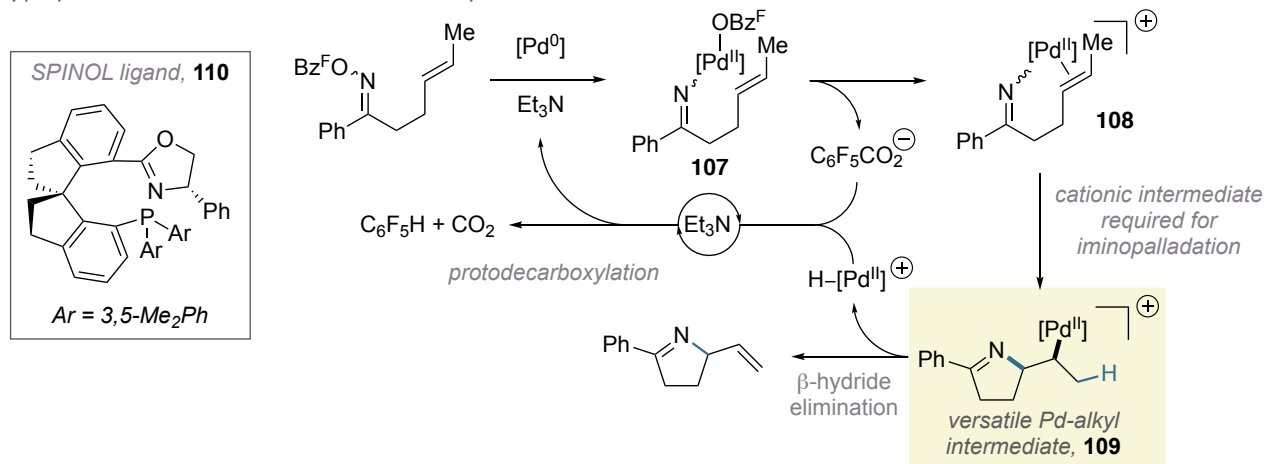
**Scheme 24** | Intermolecular Pd-catalyzed aminoacetoxylation

In 2015, Bower described an umpolung approach to intramolecular oxidative amination involving oxidative addition of a  $\text{Pd}^0$ -catalyst to an electrophilic nitrogen source (Scheme 25a). This strategy enables the amination of more hindered 1,1-disubstituted alkenes as well as cross-coupling of the resulting  $\text{Pd}$ -alkyl species with a range of suitable electrophiles<sup>141</sup>. Building upon early work by Narasaka<sup>142</sup> and Fürstner<sup>143</sup>, the use of *O*-pentafluorophenylbenzoyl oxime esters **102** proved crucial in balancing substrate stability and efficient aminopalladation; strongly polarizing groups can be prone to competing hydrolysis and rearrangements<sup>144</sup>.

## (a) Bower (2015)



## (b) proposed mechanism for oxime-ester aminopalladation

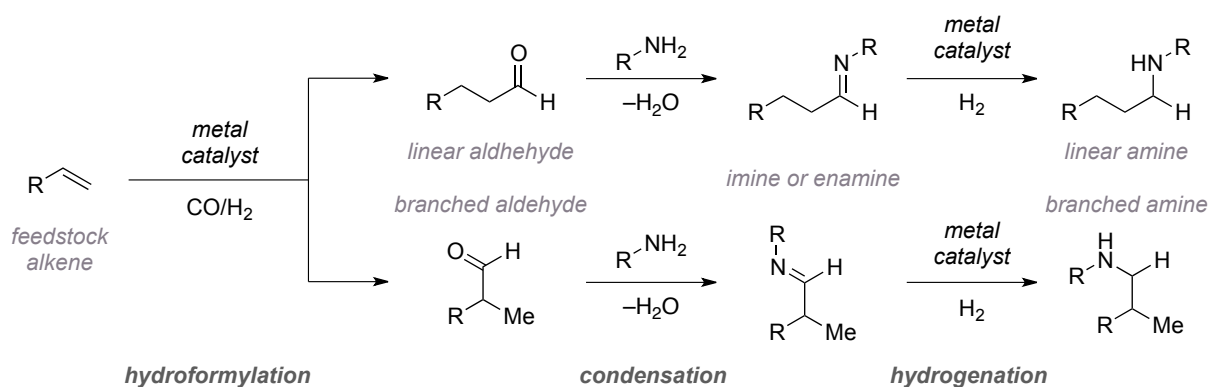


Scheme 25 | (a) Intramolecular aminopalladation of oxime esters. (b) Proposed mechanism

Upon oxidative addition into the activated N–O bond, the resulting Pd-benzoate species **107** undergoes protodecarboxylation, shifting the equilibrium towards a cationic-Pd species **108** that is critical for iminopalladation (Scheme 25b). The resulting key Pd-alkyl intermediate **109** was found to undergo aminoacylation **103** and carboxylation **104** with CO, as well as aminoarylation, vinylation and alkynylation **105** using a range of boronic esters in good yields<sup>145</sup>. Recently, Bower outlined a highly enantioselective Pd-catalyzed intramolecular Aza-Heck cyclization of challenging trisubstituted alkenes, furnishing difficult to synthesize chiral  $\alpha$ -tertiarypyrrolidine derivatives **106** in high yields and enantioselectivities using a weakly electron-donating SPINOL-derived *P,N*-ligand **110** (up to 86% yield, up to 90% e.e.)<sup>141</sup>. Moreover, in 2016 Bower reported that *N*-(pentafluorobenzoyloxy)sulfonamides could similarly undergo Pd-catalyzed Aza-Heck type cyclizations facilitated by electron-poor phosphine ligands<sup>146</sup>. Importantly, the varied substrate scope and use of hindered alkenes cannot be replicated using current oxidative Wacker approaches.

## 1.2.4 Hydroaminomethylation

From the perspective of generating complex amines via the multicomponent coupling of readily available feedstocks, hydroaminomethylation is a consummate process. The combination of CO/H<sub>2</sub> (syngas), alkene and amine, and a transition metal catalyst, enables the rapid assembly of ‘higher order’ amine products with perfect atom economy and little environmental impact. In fact, hydroaminomethylation is the net result of three successive processes: i) alkene hydroformylation; ii) condensation; and iii) hydrogenation (Scheme 26)<sup>147</sup>.



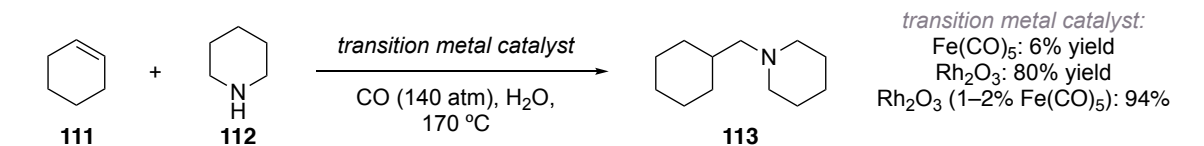
**Scheme 26** | Overview of hydroaminomethylation

Although at first glance hydroaminomethylation appears a near perfect reaction, there still remain significant hurdles to overcome in order to translate this powerful methodology into one that is part of the everyday lexicon of organic chemists. Principally, the high operating pressures and temperatures required have thus far rendered this process solely in the domain of industrial chemists. Importantly, controlling both chemoselectivity and regioselectivity concurrently is paramount in ensuring high yields of a single amine product, as fractional distillation of mixtures of isomers is both costly and challenging. The complexity of the multicomponent, three-step process often culminates in the production of unwanted side-products resulting from the hydrogenation and aldol condensation of various intermediates, lowering its overall efficiency. As such, alkene hydroaminomethylation has suffered from limited application in the synthesis of complex amines; however, significant progress has been made in recent years to overcome these challenges<sup>148–150</sup>.

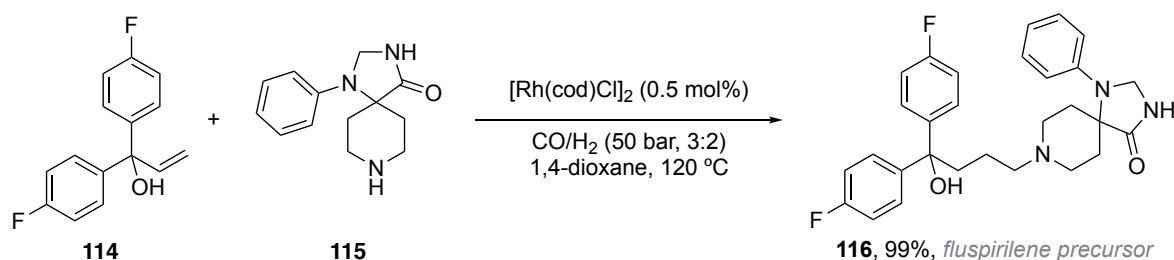
The first reported hydroaminomethylation by Reppe in 1953 utilized stoichiometric Fe(CO)<sub>5</sub> to mediate the reaction between acetylene, ammonia, and carbon monoxide and water (hydrogen source) to generate acrylamide under forcing conditions (T > 300 °C, up to 150 bar)<sup>151</sup>. Owing to its low efficiency, subsequent efforts to develop catalytic systems for hydroaminomethylation gave rise to first generation cobalt, nickel and manganese catalysts<sup>150</sup>. In 1971, Iqbal reported that by using

$\text{Rh}_2\text{O}_3$ , the hydroaminomethylation of cyclohexene **111** with piperidine **112**, generating 1-(cyclohexylmethyl)piperidine **113**, could be accomplished in a significantly improved yield (80%) compared with the  $\text{Fe}(\text{CO})_5$  system of Reppe (6%) (Scheme 27a)<sup>152</sup>.

## (a) Iqbal (1971)



## (b) Eilbracht (2004)



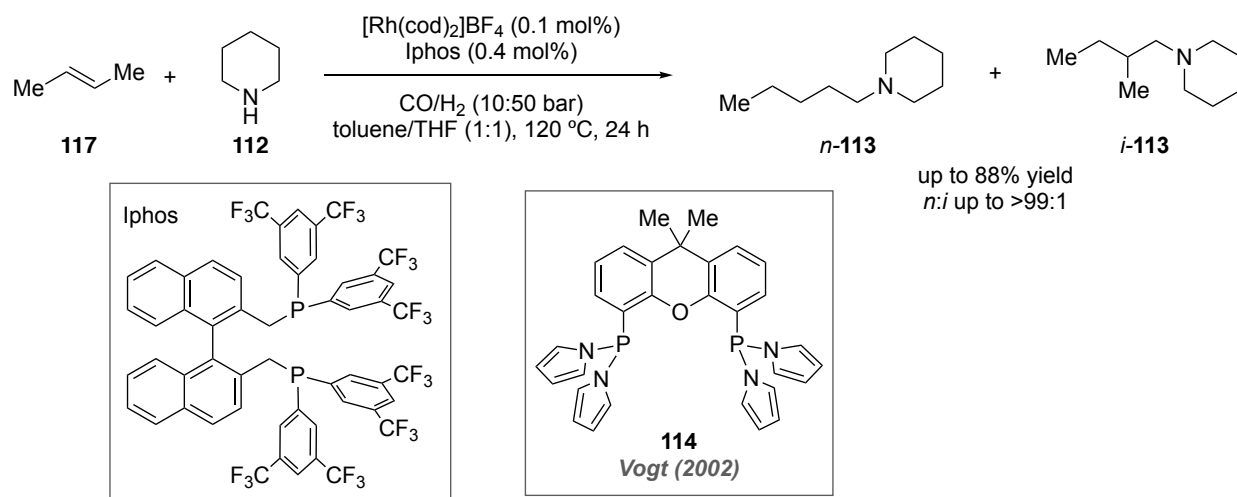
**Scheme 27** | (a) Early examples of hydroaminomethylation. (b) Complex molecule synthesis

As a result of the systematic efforts of Eilbracht in the late 1990's, significant advances in Rh-catalyzed hydroaminomethylation were achieved, bringing it to the forefront of modern amine synthesis<sup>153–155</sup>. In 2004, Eilbracht reported the hydroaminomethylation of 1,1-diaryl-allyl alcohols **114** with complex piperidines **115** for the generation of pharmaceutically relevant 4,4-diarylbutylamines using an unmodified  $[\text{Rh}(\text{cod})\text{Cl}]_2$  catalyst (Scheme 27b)<sup>156</sup>. The low catalyst loading (0.5 mol%) and milder conditions (120 °C, 50 bar) allowed, for the first time, more complex amine and alkenes to be used as substrates. The corresponding products – fluspirilene (antipsychotic) precursor **116** and diphenidiol (antiemetic), were accessed in near quantitative yield.

Despite these important advancements, efforts to enhance and moderate both the chemo- and regioselectivity have been primarily brought about through the addition of ligands<sup>157–160</sup>. Owing to their higher denticity and hence ability to greater effect the steric environment around the transition metal centre, biphosphine ligands have given rise to high levels of chemo- and regioselectivity. In 2002, Beller reported the first synthesis of linear alkylamines from internal alkenes via a tandem Rh-catalyzed isomerization/hydroaminomethylation in good yields and excellent selectivities (Scheme 28)<sup>161</sup>. The use of a sterically demanding, electron-poor Iphos biphosphine ligand was found to be essential in balancing both isomerization and selective enamine/imine hydrogenation in the presence of strongly  $\sigma$ -donating amine ligands. In this regard, the hydroaminomethylation of 2-butene **117** and piperidine **112** afforded the linear amine product **113** (*n:i* > 99:1) in 88% yield under comparatively mild conditions. Further studies by Beller showed that Xantphos was also an excellent ligand for the

isomerization/hydroaminomethylation of internal alkenes due to its flexible bite angle (*vide infra*)<sup>162,163</sup>. In addition, the electronic properties have also been shown to have a crucial influence on the activity and selectivity of hydroaminomethylation reactions. In 2002, Vogt demonstrated that bespoke bis(dipyrrolylphosphino)xanthene ligands **114** (Scheme 28), with excellent  $\pi$ -acceptor capability, facilitated CO dissociation via the trans-effect, resulting in greatly enhanced activity and selectivity (TOF up to 6200 h<sup>-1</sup>, *n*:*i* up to 200:1)<sup>164</sup>.

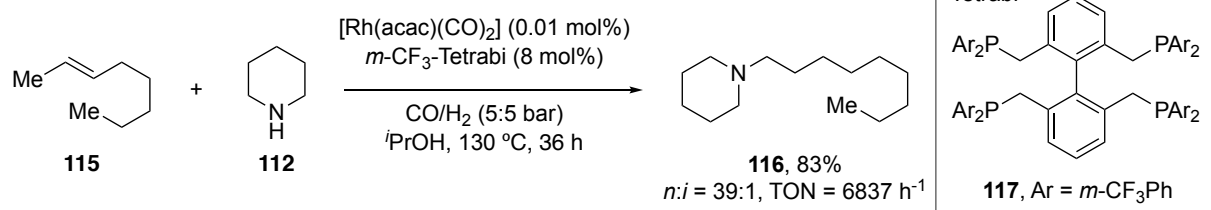
Beller (2002)



Scheme 28 | Isomerization/hydroaminomethylation of internal alkenes

In 2011, Zhang described a novel pyrrole based tetraphosphorous Tetrabi ligand for the hydroaminomethylation of alkenes and secondary alkylamines<sup>165</sup>. Due to the increased phosphine concentration around the transition metal centre, resulting in greater chelation, both the amine selectivity and regioselectivity of the hydroaminomethylation were exceptionally high (selectivity up to 99.7%, *n*:*i* > 525:1). A subsequent report in 2012 demonstrated the utility of Tetrabi-type ligands **117** in the tandem isomerization/hydroaminomethylation of internal alkenes **115** with piperidine **112**, furnishing the linear amine products **116** with high selectivity and good regioselectivity (selectivity up to 99.2%, *n*:*i* up to 96:4) (Scheme 29)<sup>166</sup>. The remarkable efficiency (TON up to 6837) and selectivity exhibited by this catalyst system ranks it amongst the best reported for hydroaminomethylation.

Zhang (2012)

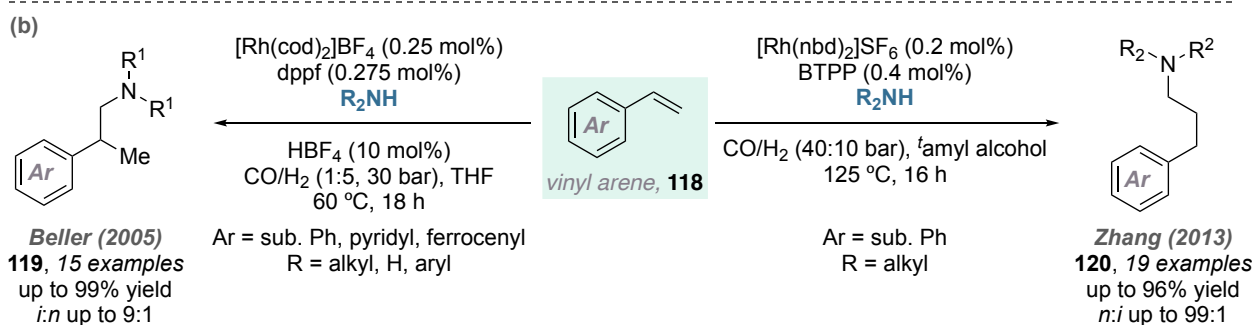
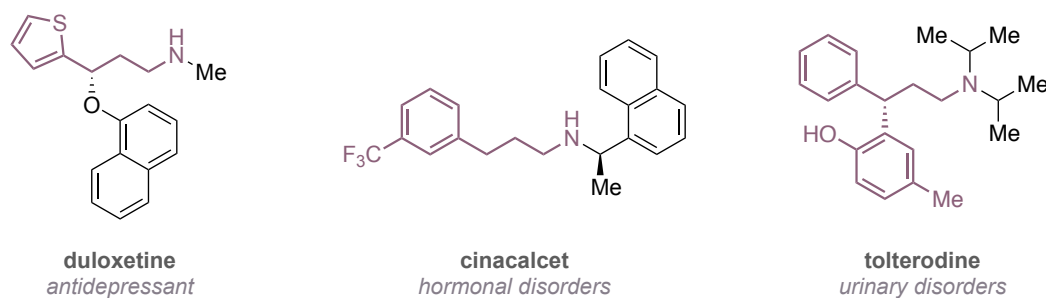


Scheme 29 | Hydroaminomethylation using tetraphosphorus ligand



The hydroaminomethylation of vinyl arenes is of great synthetic interest due to its ability to generate biologically active phenethylamines and phenpropylamines (Scheme 30a)<sup>167</sup>. However, the hydroaminomethylation of vinyl arenes often gives rise to mixtures of products, predominantly branched, due to the stability of  $\eta^3$ -benzyl species. In 2005, Beller developed a cationic Rh/DPPF-catalyzed hydroaminomethylation of vinyl arenes **118**, in the presence of HBF<sub>4</sub>, to generate the corresponding branched amines **119** with high regioselectivity (*i:n* up to 99:1) (Scheme 30b)<sup>168</sup>.

(a) pharmaceutically relevant phenpropylamines

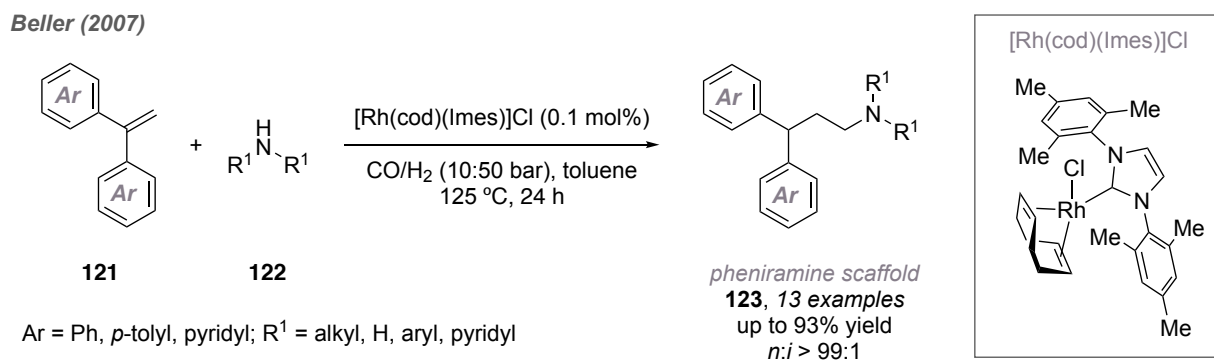


**Scheme 30** | (a) Importance of phenpropylamines. (b) Linear and branch selective hydroaminomethylation

Although the exact role of the acid is not clear, it most likely accelerates hydrogenation by protonation of the imine – forming the more reactive iminium ion. In 2013, Zhang reported the first general hydroaminomethylation strategy for the selective formation of linear phenpropylamines **120** from vinyl arenes **118** (Scheme 30b)<sup>169</sup>. Using a strong  $\pi$ -accepting and sterically hindered tetraphosphorus dipyrrolylphosphoramidite ligand, BTTP, in combination with catalytic  $[Rh(nbd)_2]SbF_6$ , unprecedented levels of selectivity (*n:i* up to >99:1) for the linear amine could be achieved.

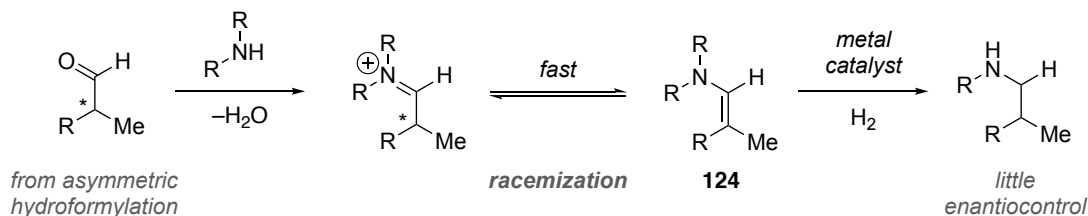
In order to combat the issue of phosphine ligands reducing the hydrogenation activity of Rh/P-catalyzed hydroaminomethylation systems, Beller proposed the use of a well-defined Rh-monocarbene complex. In 2003, the first report of hydroaminomethylation using preformed  $[Rh(cod)(Imes)]Cl$  was described, achieving high levels of activity<sup>170</sup>. However, achieving good regioselectivity for simple terminal alkenes proved challenging. Nonetheless, in 2007 Beller reported

that by using the same catalyst system, the hydroaminomethylation of previously intractable 1,1-diphenylethenes **121** with secondary amines **122** could be accomplished, yielding 3,3-diarylpropylamines (pheniramines) **123** – an important class of first generation H<sub>1</sub>-antihistaminic drugs<sup>171</sup>. High yields and excellent selectivities (*n:i* up to 99:1) were reported with comparatively low catalyst loading and mild reaction conditions (Scheme 31). Similar efficiencies have been recently reported by Zhang using a Rh/Naphos-catalyst system under similarly mild conditions for the hydroaminomethylation of 1,1-diphenylethenes<sup>172</sup>.



**Scheme 31** | Rh-carbene catalyzed hydroaminomethylation

Given the plethora of chiral amines among pharmaceutical agents<sup>1</sup>, the synthesis of these important molecules via enantioselective hydroaminomethylation appears particularly attractive. However, perhaps the most challenging obstacle to overcome is the unavoidable racemization of the chiral iminium intermediate via tautomerization to the achiral enamine **124** (Scheme 32).

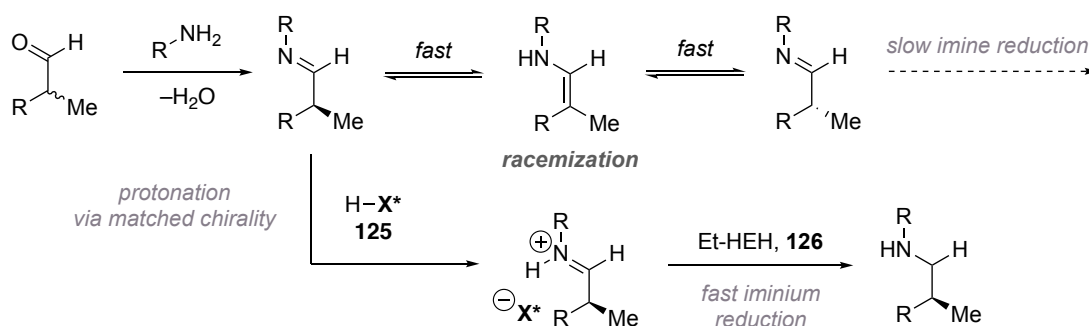


**Scheme 32** | Challenges for asymmetric hydroaminomethylation

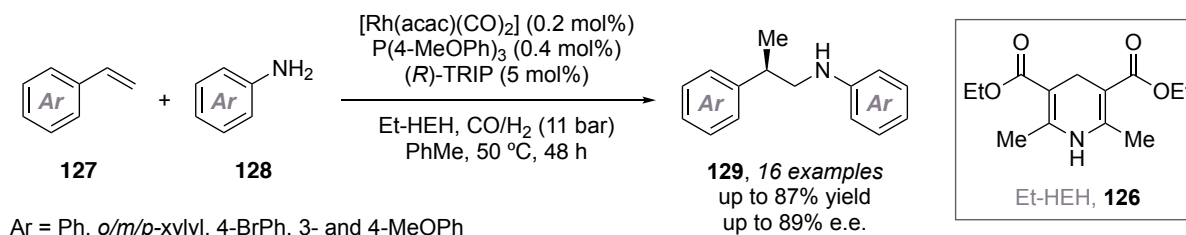
A recent study by Kalck using a host of chiral biphosphine ligands revealed no induction of stereochemistry, which was confirmed by computational studies eluding to near isoenergetic pathways for the (*E*)- and (*Z*)-enamine hydrogenation, irrespective of the chirality of the ligands<sup>173</sup>. Moreover, the reductive elimination of the final product also proved to be rate limiting. In light of these challenges, an alternative strategy was put forward by Xiao reasoning that a hydroaminomethylation reaction could be rendered enantioselective if the final enamine can be hydrogenated via a potentially different asymmetric pathway (Scheme 33a)<sup>174</sup>. As such, a combined metal/organocatalytic framework was established whereby initial racemic Rh-catalyzed hydroformylation of vinyl arenes **127** with anilines **128** occurred regioselectively, affording the

branched aldehyde. Subsequently after condensation, a combination of catalytic chiral Brønsted acid (TRIP) **125** and Hantzsch ester (HEH) **126**, as a hydride source, afforded the chiral amine products **129** in good yields (up to 87%) and enantioselectivities (up to 91% e.e.) (Scheme 33b). In 2017, a related tandem asymmetric hydroaminomethylation using a similar Rh-catalyst and TRIP/HEH reduction was reported by Han using exceedingly mild conditions (25 to 50 °C and 1 bar pressure)<sup>175</sup>. Excellent yields and enantioselectivities were achieved for the hydroaminomethylation of vinyl arenes with primary anilines, as well as for a series of aliphatic alkenes, acrylamides and vinyl esters (up to 89% e.e.).

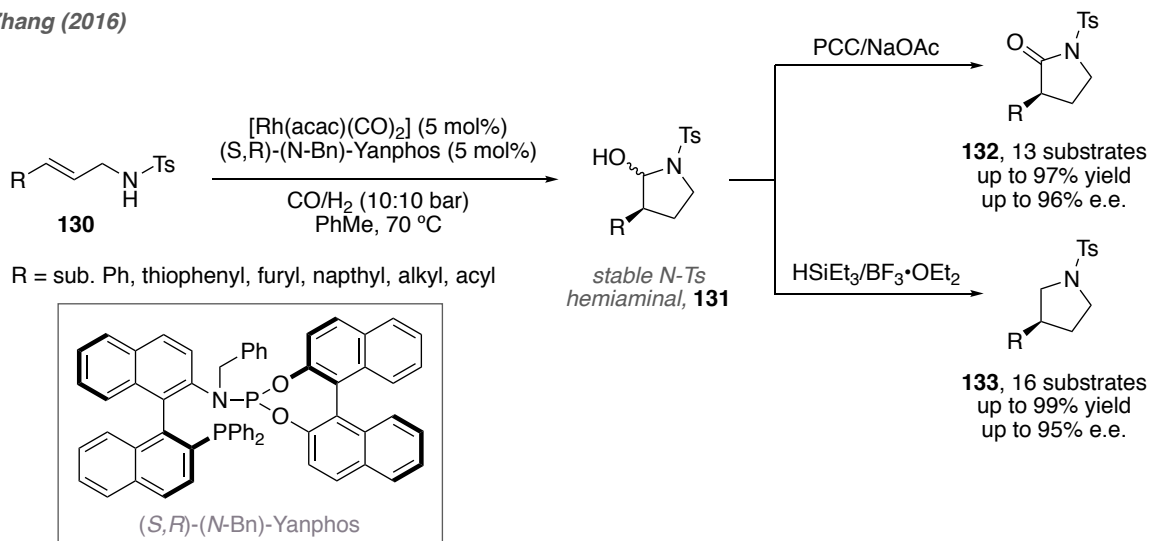
(a) strategy for dual Rh/organocatalytic asymmetric hydroaminomethylation



(b) Xiao (2015)



(c) Zhang (2016)

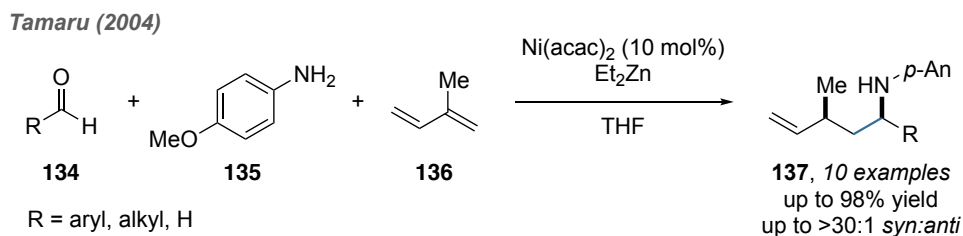


**Scheme 33** | (a) Design plan for asymmetric hydroaminomethylation. (b) Chiral phosphoric acid mediated. (c) Chiral biphosphine ligand mediated

A recent interesting report by Zhang described an interrupted asymmetric intramolecular hydroaminomethylation for the synthesis of chiral 3-arylpyrrolidines (Scheme 33c)<sup>176</sup>. Using a chiral Yanphos ligand, intramolecular enantioselective hydroformylation of unsaturated tosylamides **130** led to the formation of a stable hemiaminal **131**, which upon oxidative or reductive work-up, furnished the corresponding lactams **132** or pyrrolidines **133** in good yields and enantioselectivities (up to up to 99% yield, up to 96% e.e.).

### 1.2.5 Hydroaminoalkylation

Despite notable advances, hydroaminomethylation is fundamentally limited to the use of carbon monoxide as a C<sub>1</sub>-source; therefore, the use of supplementary carbonyl feedstocks would significantly enhance the utility of this reaction. Late transition metal catalyzed hydroaminoalkylation constitutes a valuable alternative, whereby a preformed imine and alkene are reductively coupled, forging a new C(sp<sup>3</sup>)-C(sp<sup>3</sup>) bond. Important early catalytic work by Morken<sup>177</sup>, Matsuda<sup>178</sup>, Shibasaki<sup>179</sup> and Trost<sup>180</sup> have been limited to the use of activated alkenes such as  $\alpha,\beta$ -unsaturated carbonyl systems, enol-derived alkenes as well as reactive allylic boranes and silanes. In comparison, the use of unactivated alkenes as the  $\pi$ -coupling partner has been far less explored, principally due to their low reactivity<sup>181</sup> and propensity to undergo aza-Diels Alder cycloadditions instead of forming linear products<sup>182</sup>. In 2004 Tamaru reported the highly stereo- and regioselective Ni-catalyzed homoallylation of aldimines with conjugated 1,3-dienes (Scheme 34)<sup>183</sup>. Usefully, the condensation between various alkyl and aryl aldehydes **134** and *p*-anisidine **135** could be accomplished *in-situ*; the subsequent addition of Ni(acac)<sub>2</sub>, isoprene **136** and Et<sub>2</sub>Zn as the reductant (H-donor) afforded the 1,3-*syn* products in good yields and high diastereoselectivities (up to 98% yield, up to >30:1 *syn:anti*).

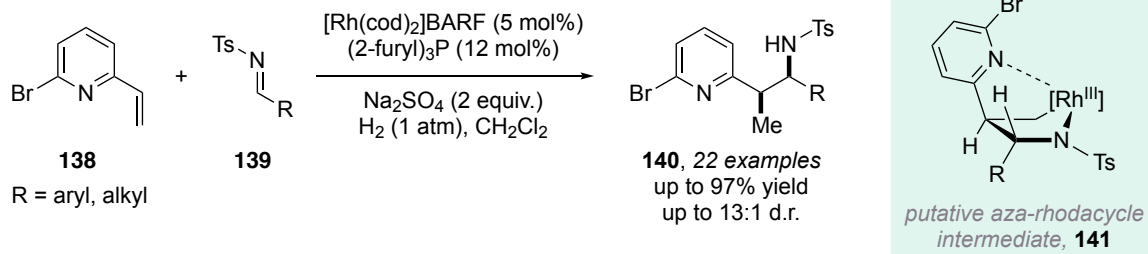


**Scheme 34** | Ni-catalyzed multicomponent synthesis of secondary aryl amines

In 2008, Krische detailed the first Rh-catalyzed reductive coupling of *N*-tosylaldimines **139** and vinyl azines **138** in good yields and reasonable levels of *syn*-diastereoselectivity (up to 97% yield, up to 13:1 d.r.) (Scheme 35)<sup>184</sup>. Mechanistic studies using a [Rh(cod)<sub>2</sub>]BArF catalyst alongside a

trifurylphosphine ligand and hydrogen as the net reductant, revealed that coupling of the vinyl azine and imine delivers a cationic aza-rhodacyclopentane **141** that undergoes subsequent hydrolytic cleavage to generate the heteroaryl-amine products **140**.

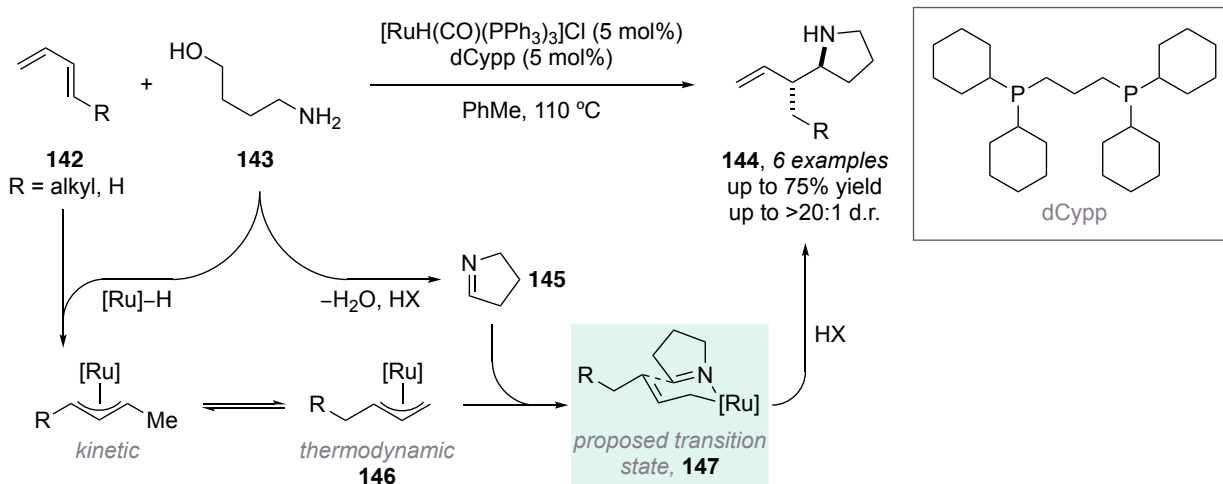
Krische (2008)



**Scheme 35** | Reductive coupling of vinyl azines and N-tosyl imines

Inspired by the analogous Ru-catalyzed redox-triggered transfer hydrogenation between alcohols and  $\pi$ -unsaturated systems<sup>185</sup>, termed hydrohydroxyalkylation, Krische described the C–C coupling of amino alcohols with 1,3-dienes to generate complex pyrrolidines (Scheme 36)<sup>186</sup>. Accordingly, Ru-mediated transfer hydrogenation of 4-aminobutanol **143**, at oxygen, and butadiene **142** results in the pairwise formation of a cyclic Schiff base **145** and  $\pi$ -allyl Ru-complex **146**. Subsequent combination of these species, via a chair-like transition state **147**, results in the products of formal hydroaminoalkylation **144**. Using a  $[\text{RuH}(\text{CO})(\text{PPh}_3)_3]\text{Cl}$  catalyst and dCypp ligand, the products akin to that of imine *anti*-crotylation, could be obtained in good yields and excellent *anti*-diastereoselectivity (up to 75% yield, up to >20:1 d.r.).

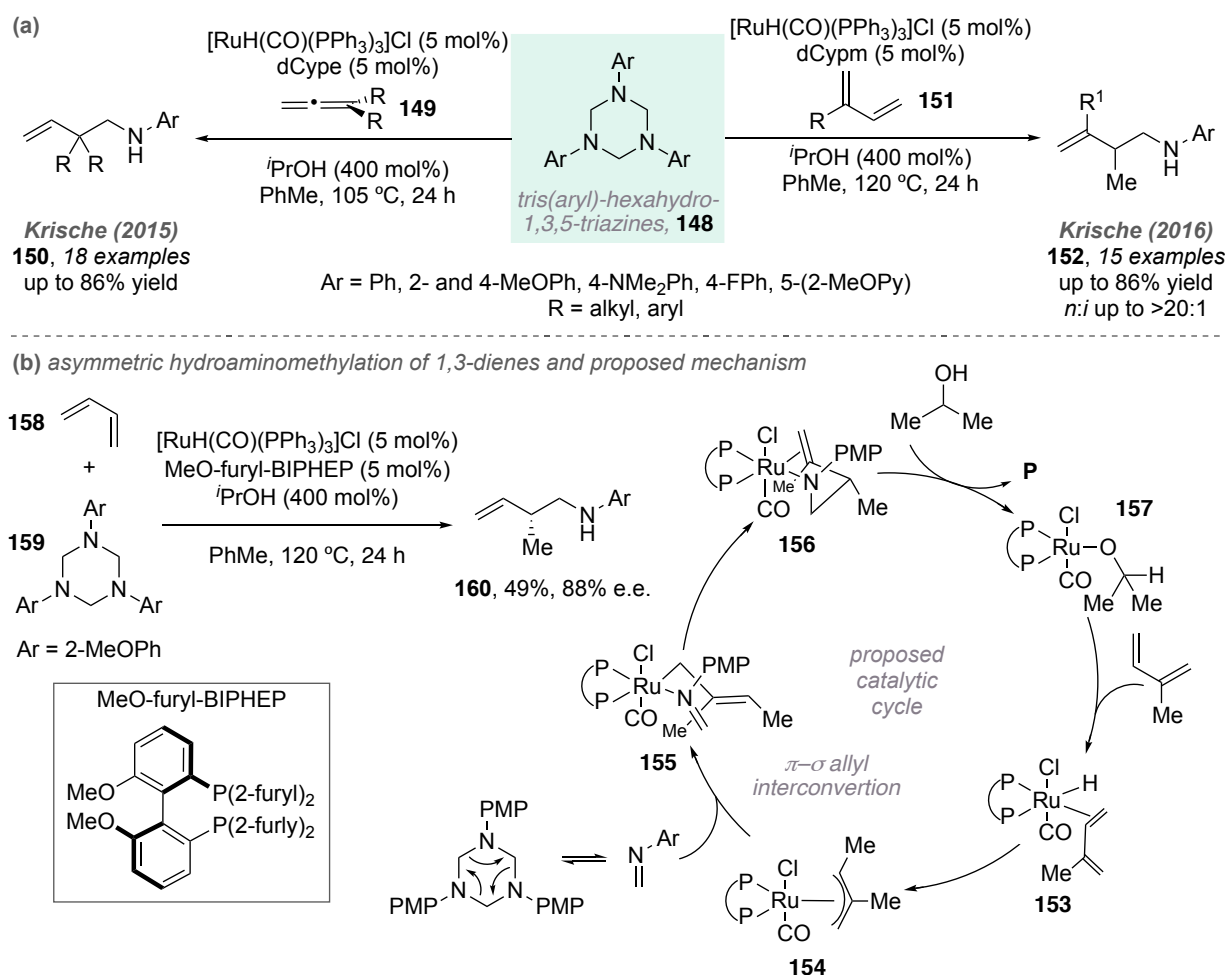
Krische (2015)



**Scheme 36** | Redox triggered transfer hydrogenation of aminoalcohols and 1,3-dienes

In 2015, Krische further explored the use of tris(aryl)-hexahydro-1,3,5-triazines **148** as stable formaldehyde-imine surrogates for use in the hydroaminoalkylation of 1,1-disubstituted allenes **149** (Scheme 37a)<sup>187</sup>. Again employing a  $[\text{RuH}(\text{CO})(\text{PPh}_3)_3]\text{Cl}$  catalyst and dCype ligand, alongside isopropanol as a reductant, the branched amine products **150**, bearing all-carbon quaternary centres,

were furnished in good yields (up to 86%). The following year, the scope was expanded to include the hydroaminoalkylation of 1,3-dienes **151**, delivering homoallylic amines **152** in similar yields and excellent regioselectivities (up to 86% yield, up to >20:1 *n:i*) (Scheme 37a)<sup>188</sup>. Mechanistically, diene hydorruthenation generates a  $\pi$ -allylruthenium complex **154**, which undergoes rearrangement to the more thermodynamically favourable *cis*-substituted  $\sigma$ -allyl intermediate **155** (Scheme 37b). Coordination of the imine and turn-over limiting addition occurs via a highly organised 6-membered transition state. Successive protonolysis of the amido–Ru species **156** with isopropanol and  $\beta$ -hydride elimination (from **157**) affords the Ru–H catalyst **153**. The highly ordered-transition state gave way to an enantioselective modification using an axially chiral biphenyl ligand, MeO-furyl-BIPHEP (Scheme 37b). Despite modest conversion to the chiral homoallyl amine **160**, the hydroaminomethylation of butadiene **158** with 2-methoxyaniline (from triazine **159**) proceeded with good enantioselectivity (88% e.e.).

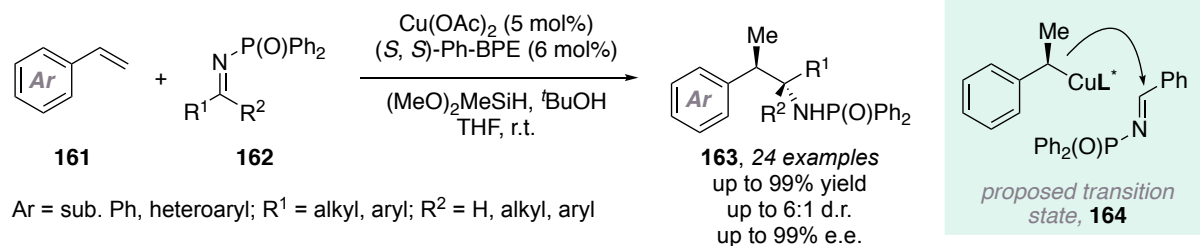


**Scheme 37** | (a) Reductive coupling of triazine-derived imines with allenes and 1,3-dienes. (b) Proposed mechanism and asymmetric coupling

In 2016, Buchwald described the intermolecular Cu-catalyzed enantioselective addition of styrenes **161** to protected imines **162** (Scheme 38). Employing a combination of Cu(OAc)<sub>2</sub>/(*S,S*)-Ph-BPE and

(MeO)<sub>2</sub>MeSiH, asymmetric hydrocupration of the vinyl arene, followed by addition to the imine **164**, furnishes the products upon protonolysis with *tert*-BuOH. The reaction proved tolerant of a range of vinyl arenes and heteroarenes, as well as alkyl and aryl substituted aldimines and ketimines, delivering the corresponding phenethylamines **163** in good yields and enantioselectivities (up to 95% yield, up to 6:1 d.r., up to 99% e.e.)<sup>189</sup>.

Buchwald (2016)



**Scheme 38** | Asymmetric reductive coupling of vinyl arenes and *N*-phosphoryl imines

### 1.3 Transition metal catalyzed C(sp<sup>3</sup>)-H functionalization

#### 1.3.1 Nitrene insertion

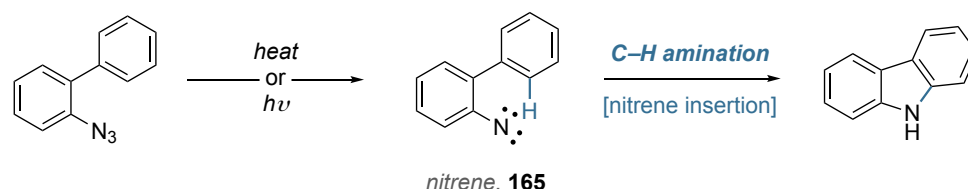
Nitrenes **165**, the nitrogen analogue of a carbene, are highly reactive intermediates comprised of a nitrogen atom bearing five valence electrons (Scheme 39a). The electron-poor nature of these species renders them powerful two-electron oxidants, giving rise to a host of unique C–N bond-forming reactions. While early work pioneered the generation of these reactive entities from the photo- and thermochemical degradation of azides<sup>190,191</sup>, the scope of nitrene insertion reactions has been significantly expanded in recent years with the concurrent advent of metal catalyzed nitrene insertions<sup>192</sup> and iminoiodanes as nitrene precursors<sup>193,194</sup>. In addition to C(sp<sup>3</sup>)-H bond amination, considerable efforts have been made in the field of C(sp<sup>2</sup>)-H amination and aziridination<sup>195–198</sup>.

The pioneering work of Breslow and Gellman demonstrated that several transition metals were capable of catalysing the intramolecular amidation of 2,5-diisopropylbenzenesulfonamide **166** from the pre-formed imidoiodo derivative **167**, generating sultams **168** (Scheme 39b)<sup>193</sup>. Amongst the metals tested, simple porphyrinoid complexes of both Mn<sup>199</sup>, Fe<sup>200,201</sup>, and Co<sup>202</sup> proved capable catalysts, albeit with moderate efficiency and the concomitant formation of dehydration side-products. However, the fact that these metals are cheap, abundant and environmentally benign has led to the development of more capable catalytic systems. Notable advances include both iron and manganese phthalocyanine complexes **171** developed by White, which show remarkable selectivity

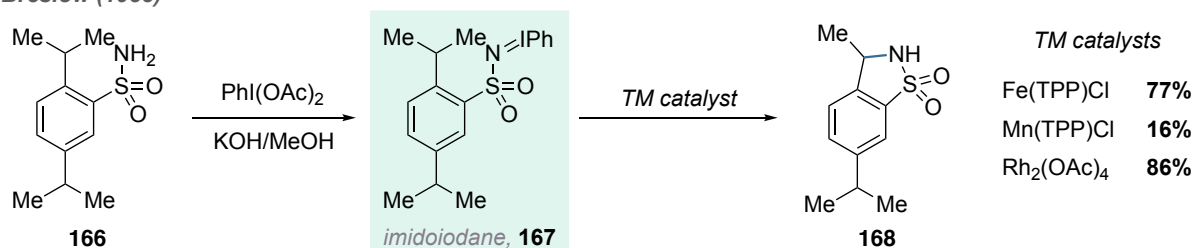


for the C–H amination of sulfamates **169**, generating the corresponding dioxoxathiazinanes **170**, even in the presence of  $\pi$ -acidic alkenes (Scheme 39c)<sup>203</sup>. Additionally, a number of non-heme based Fe-catalysts have been reported by the Betley group capable of catalyzing the intermolecular C–H amination of toluene and cyclohexene<sup>204,205</sup>.

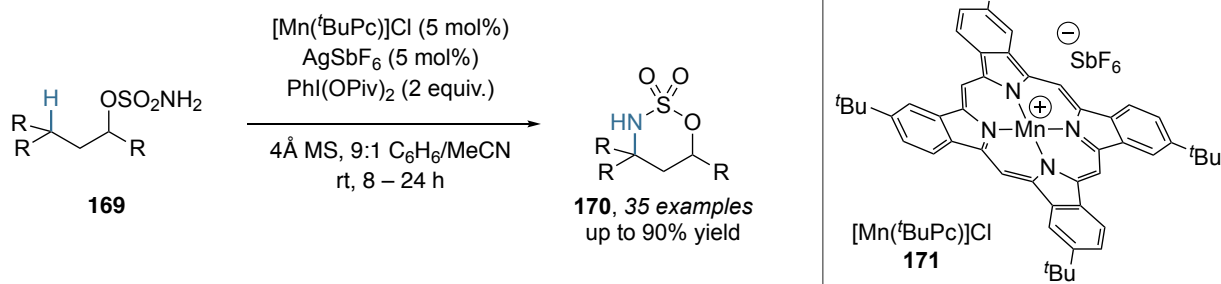
(a) nitrenes as reactive intermediates



(b) Breslow (1983)



(c) White (2015)

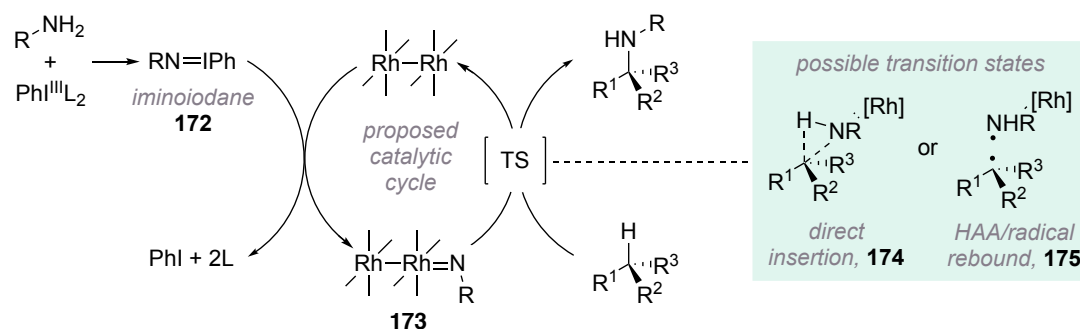


**Scheme 39** | (a) Nitrenes as reactive intermediates. (b) Early investigations. (c) Mn-porphyrinoid catalyzed C–H amination

Despite these advances, considerable developments have been made in the field of Rh-catalysis<sup>206</sup>. This has been reinforced by several mechanistic studies that have shown Rh-nitrene species, generated from the reaction between iminoiodanes and a Rh<sup>II</sup>-catalyst, undergo stereospecific C(*sp*<sup>3</sup>)–H bond insertion (Scheme 40)<sup>207,208</sup>. It is proposed that amination is initiated by the combination of the amide species, *e.g.* sulfamate, and the external oxidant, *e.g.* PIDA, to generate the iminoiodane **172**; however, limited direct evidence for the generation of this species exists to date<sup>209</sup>. Coordination of the putative iminoiodane to the Rh-catalyst promotes extrusion of iodobenzene and generation of the active Rh-nitrenoid **173**. The precise mechanism of the C–N bond forming step has been widely debated; direct nitrene insertion **174** is the most widely accepted pathway, however recent computational evidence suggests both substrate and catalyst dependence whereby hydrogen atom abstraction (HAA)/radical rebound **175** cannot be ruled out<sup>210</sup>.



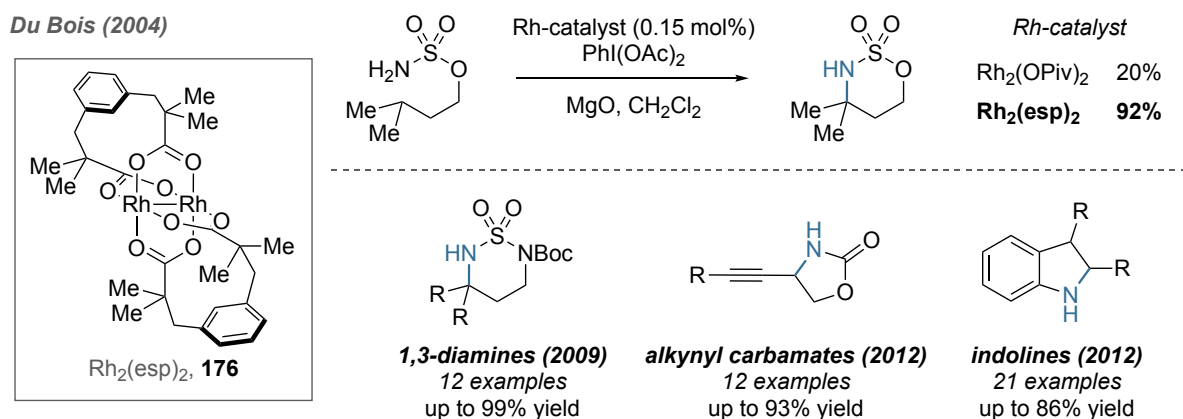
general mechanism for Rh-catalyzed C(sp<sup>3</sup>)-H amination



**Scheme 40** | Mechanistic overview for Rh-catalyzed C–H amination

The early achievements in forming iminoiodanes from the *in-situ* reaction of PIDA and a primary amide dramatically improved the scope of C–H amination reactions using Rh-carboxylate catalysts<sup>211</sup>. The presence of an electron-withdrawing group on the nitrogen was not only crucial for reactivity, but also determined the selectivity; carbamates and ureas preferred cyclization to afford the 5-membered ring product, whereas larger sulfamates, sulfamides and phosphoramidates favoured 6-membered ring cyclization<sup>212</sup>. Various studies assessing the chemoselectivity in intramolecular processes revealed the following trend: 3° > α-oxy, α-amino, benzylic > 2° >> 1°<sup>207</sup>. Furthermore, the cyclizations typically proceeded with high levels of diastereoselectivity in line with a chair-like transition state, in which the substituents adopt a pseudo-equatorial arrangement minimizing A-strain<sup>213</sup>. As a result of the predictable reactivity, the intramolecular C–H amination has been used to great effect in a variety of elegant total synthesis<sup>214</sup>, including that of saxitoxin<sup>215</sup> and tetrodotoxin<sup>216</sup> by Du Bois.

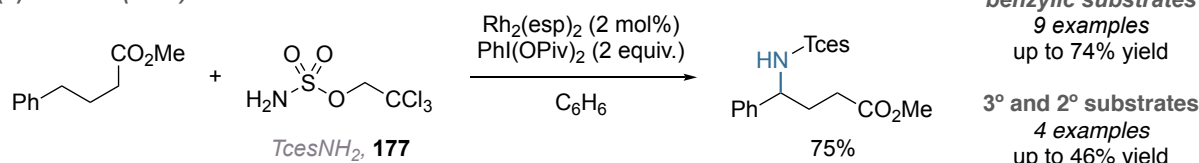
In spite of these efforts, it was well established that simple Rh-carboxylate complexes, *e.g.* Rh<sub>2</sub>(OPiv)<sub>4</sub>, underwent rapid ligand exchange under the reaction conditions, leading to catalyst degradation<sup>217</sup>. Although beneficial effects were found through the use of MgO as an additive to scavenge the acetic acid by-product<sup>211</sup>, resulting from the amide oxidation, solving the problem of catalyst stability still remained an important challenge. In 2004, Du Bois reported an elegant solution to this problem through the use of a tethered dicarboxylate-derived Rh-complex, Rh<sub>2</sub>(esp)<sub>2</sub> **176** (Scheme 41)<sup>218</sup>. The catalyst proved to be remarkably resilient towards degradation and offered far superior catalytic activity for more challenging 2° C–H bonds, as well as greater functional group compatibility when compared to Rh<sub>2</sub>(OPiv)<sub>4</sub> and Rh<sub>2</sub>(TPA)<sub>4</sub>. As a result, Rh<sub>2</sub>(esp)<sub>2</sub> has found numerous applications including the diastereoselective synthesis of *anti*-1,3-diamines<sup>219</sup>, the amination of propargylic C–H bonds to form alkynyl carbamates<sup>220</sup>, and the decomposition/cyclization of aryl azides to form indolines (Scheme 41)<sup>221</sup>.



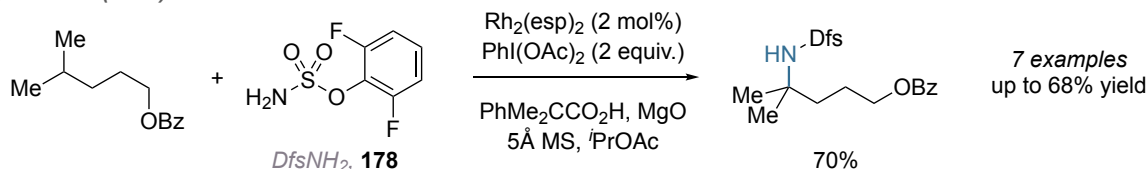
**Scheme 41** | Development and scope of Rh-catalysts for C–H amination

Although great progress has been made towards the development of intramolecular amination, the corresponding intermolecular process has long suffered from low conversion and the need for large excesses of alkane substrate (up to 100 equivalents)<sup>222</sup>. In 2007, Du Bois reported a pioneering example of  $\text{Rh}_2(\text{esp})_2$ -catalyzed intramolecular amination whereby the starting alkane served as the limiting component. Crucially, the use of electron-deficient trichloroethylsulfamate ( $\text{TcesNH}_2$ ) **177** was necessary in delivering the aminated product in high yield, alongside the more soluble  $\text{PhI}(\text{OPiv})_2$  (Scheme 42a)<sup>222</sup>. The reaction proved remarkably selective for benzylic C–H bonds; however, similarly reactive 3° C–H bonds surprisingly afforded the desired product in low yield. The poor efficiency of 3° C–H amination was attributed to unfavourable steric interactions between the congested tertiary centre and large catalyst, resulting in deleterious side reactions, including oxidation of the methylene centre of trichloroethylsulfamate. For this reason, in 2013 Du Bois reported that electron-poor 2,6-difluorophenoxysulfonamide ( $\text{DfsNH}_2$ ) **178** was capable of undergoing intermolecular Rh-catalyzed amination of 3° C–H bonds with high efficiency (Scheme 42b)<sup>223</sup>. Notably, excellent selectivity was observed even in the presence of multiple 3° C–H bonds. Recently, Du Bois reported a streamlined procedure the intermolecular  $\text{Rh}_2(\text{esp})_2$ -catalyzed C–H amination of complex molecules and pharmaceuticals (Scheme 42c)<sup>224</sup>. Using phenoxysulfonamide as a simple aminating agent, the use of pivaloylnitrile ( $^t\text{BuCN}$ ) afforded a substantial improvement in terms of scope and catalyst efficiency.

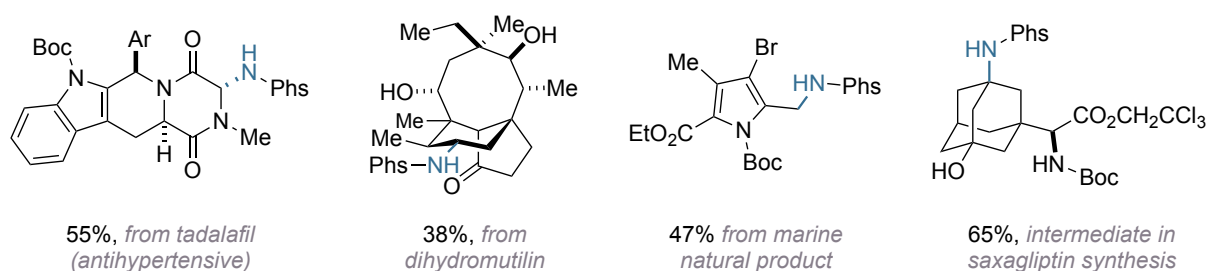
## (a) Du Bois (2007)



## (b) Du Bois (2013)



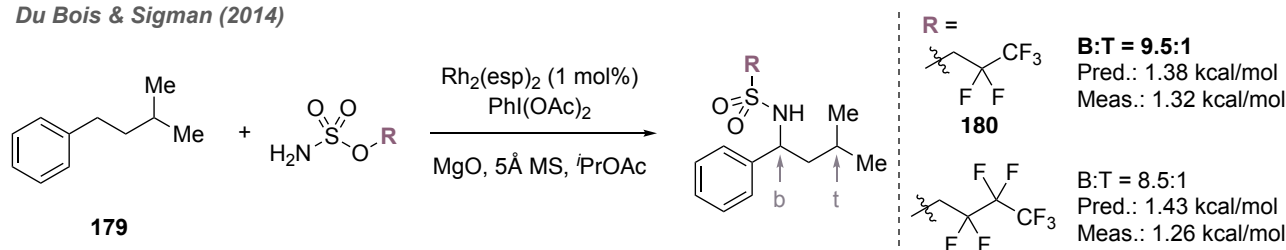
## (c) complex molecule C–H amination (Du Bois, 2018)



**Scheme 42** | (a) Intermolecular benzylic C–H amination. (b) 3° Selective C–H amination. (c) Complex molecule amination

Despite the recent advancements in intermolecular C–H amination, the selectivity often remains poor when multiple reactive sites are present. Isoamylbenzene **179** is an archetypal example whereby the benzylic to tertiary (B:T) ratio is highly dependent on the sulfamates ester used<sup>223</sup>. In 2014, Du Bois and Sigman reported a detailed site-selectivity analysis using a combination of classical Hammett parameters and computed IR vibrational data (Scheme 43)<sup>225</sup>. By way of a training set, a library of 23 sulfamate esters were tested with isoamylbenzene and the B:T ratios measured. The model was subsequently tested against 38 external validation substrates and the information extrapolated to predict new sulfamates esters that would exhibit high B:T selectivity. Based on this, pentafluoropropyl sulfamate **180** was found to give 9.5:1 B:T selectivity upon reaction with isoamylbenzene, the highest ratio recorded to date.

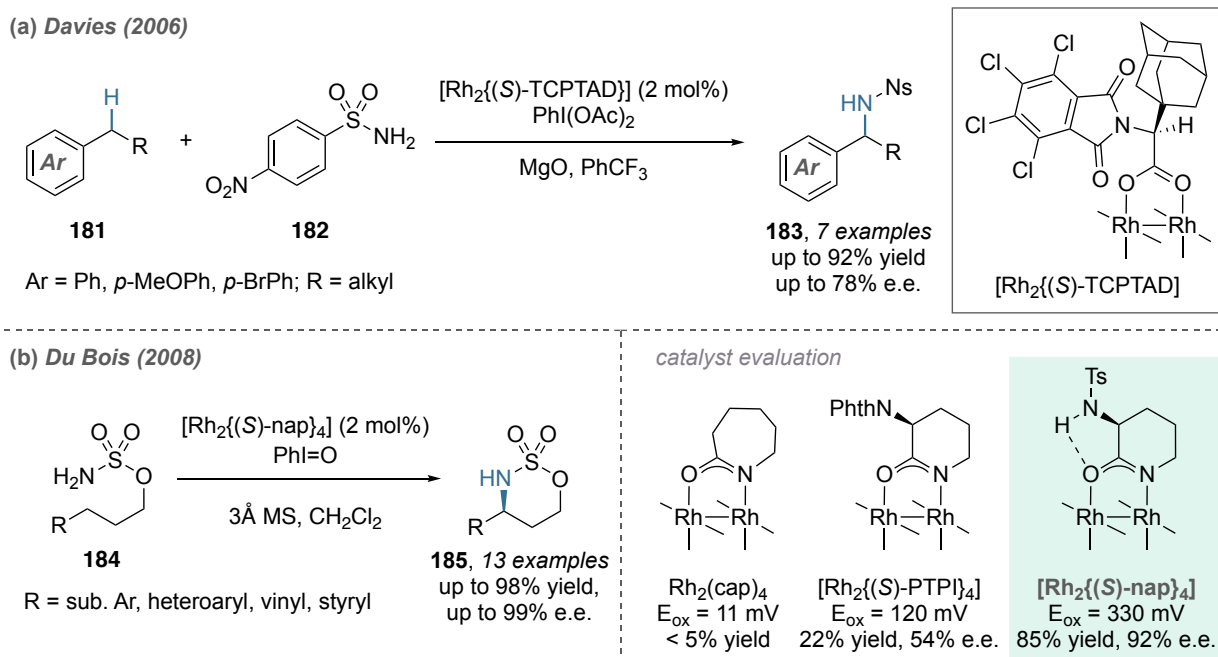
## Du Bois &amp; Sigman (2014)



**Scheme 43** | Selectivity study for benzylic C–H amination

Alongside the advancements in intra- and intermolecular C–H amination, remarkable progress has been made in the corresponding asymmetric process. Seminal work by Dauban<sup>226,227</sup> and Lebel<sup>228,229</sup>

described the diastereoselective intermolecular C–H amination of chiral sulfonimidamides using a Rh-naphthoyl-*tert*-leucine (nttl) catalyst. Both high yields and excellent chemo- and diastereoselectivities (up to 93% yield, up to >99% d.e.) were reported for a variety of benzylic and allylic substrates, notably without any competing aziridination. In 2006, Davies reported an impressive intermolecular C–H amination using *p*-nitrobenzenesulfonamide **182** and a chiral *N*-(tetrachlorophthalimido)-adamantylglycine [Rh-*{(S)-TCPTAD}*] catalyst, furnishing chiral benzylamines **183** (Scheme 44a)<sup>230</sup>. Notably, the chlorinated-phthalimido ligand gave significantly higher enantioselectivities than the parent phthalimide ligand. Good yields and good enantioselectivities were obtained for indane and tetralin based substrates **181** with excellent benzylic selectivity (up to 95% yield, up to 94% e.e.). Importantly, the scope was further elaborated to include the intramolecular C–H amination of *N*-tosyloxycarbamates to form chiral oxazolidinones in good yields and good to moderate enantioselectivities.

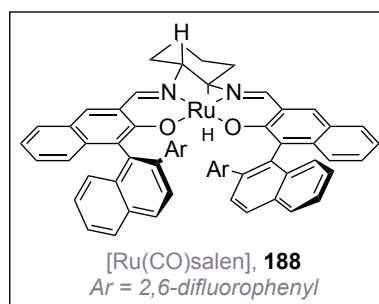
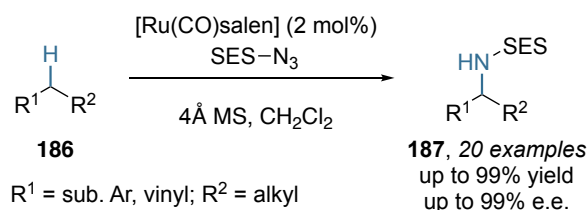


**Scheme 44** | (a) Asymmetric intermolecular C–H amination. (b) Asymmetric intramolecular C–H amination

In 2008, Du Bois reported a strategy for the asymmetric intramolecular C–H amination of sulfamates **184** (Scheme 44b)<sup>231</sup>. Based on a piperidinoate catalyst system designed by Hashimoto for cyclopropanation  $[\text{Rh}_2(\text{cap})_4]$ <sup>232</sup>, fine-tuning of the ligand electronics via a key tosylamide H–bond gave rise to an effective catalyst system  $[\text{Rh}_2\{(\text{S})\text{-nap}\}_4]$ , capable of delivering both high yields and enantioselectivities of the dioxooxathiazinane products **185** (up to 98% yield, up to 99% e.e.). A particularly striking feature of this catalyst system is the excellent chemoselectivity displayed for allylic C–H bonds (up to > 20:1), given that the closely related phthalimido ligand  $[\text{Rh}_2\{(\text{S})\text{-PTPI}\}_4]$  without a H–bond afforded primarily the aziridine product.

Alongside the advancements in Rh-catalyzed nitrene transfer, notable efforts using other second- and third-row transition metals have been described including Ag<sup>233–236</sup>, Ir<sup>237,238</sup> and Au<sup>239</sup>. In 2013, Katsuki detailed a highly regio- and enantioselective intermolecular benzylic and allylic (**186**) C–H amination using a Ru(CO)-salen complex **188** and SES azide as nitrene precursor (Scheme 45)<sup>240</sup>. Amongst reported procedures, the high yields and enantioselectivities of the amine products **187** (up to 99% yield, up to 97% e.e.) renders this one of the most effective protocols detailed to date.

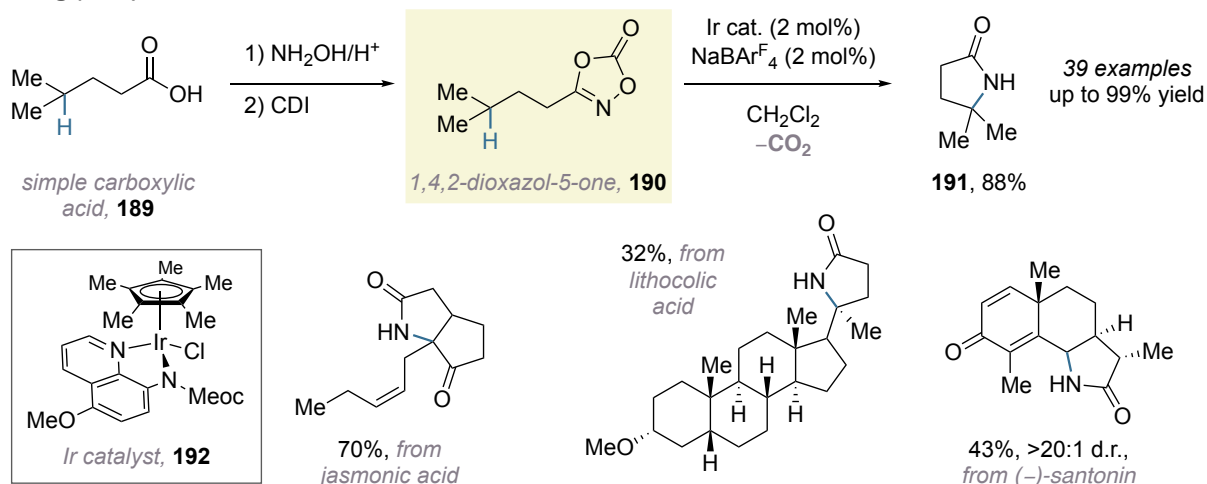
Katsuki (2013)



Scheme 45 | Intermolecular Rh-catalyzed asymmetric C–H amination

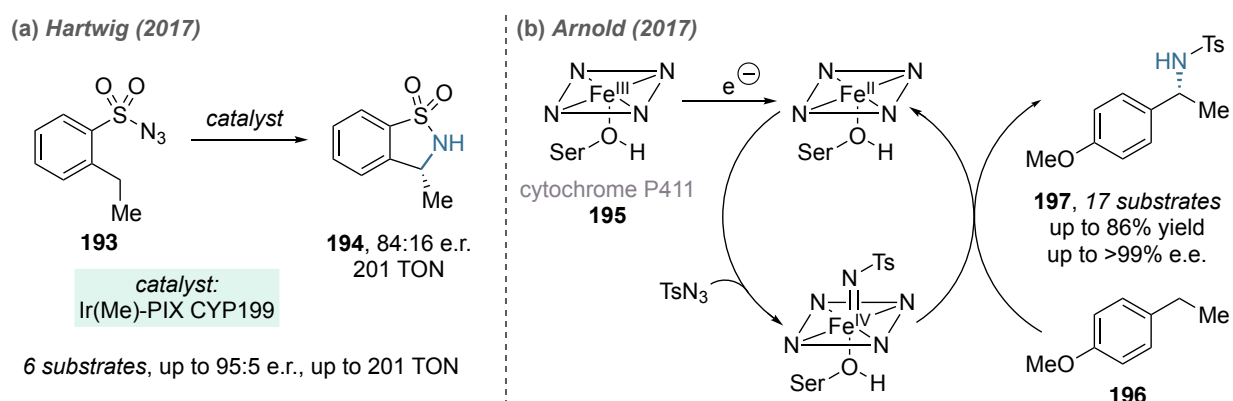
A recent report by Chang described the first intramolecular insertion of nitrenes into C–H bonds to form  $\gamma$ -lactams (Scheme 46)<sup>241</sup>. Derived in two steps for carboxylic acids **189**, the intermediate 1,4,2-dioxazol-5-ones **190** proved to be versatile precursors that, in combination with a bespoke Cp\*Ir-catalyst **192**, form the corresponding lactam products **191** with extrusion of CO<sub>2</sub> in good yields and no competing isocyanate formation. The substrate scope was particularly varied displaying broad functional group tolerance as well as activating 1°, 2°, 3° and allylic C–H bonds in good yields without accompanying aziridination.

Chang (2018)

Scheme 46 | C–H amination for the synthesis of  $\gamma$ -lactams from carboxylic acids

In 2017, Hartwig demonstrated that a cytochrome P450 containing an Ir(Me)-PIX cofactor was capable of catalyzing the intramolecular asymmetric amination of benzylic C–H bonds (**193**) (Scheme 47a)<sup>242</sup>. Although the artificial iridium metalloenzyme showed good turnover (~300 TON)

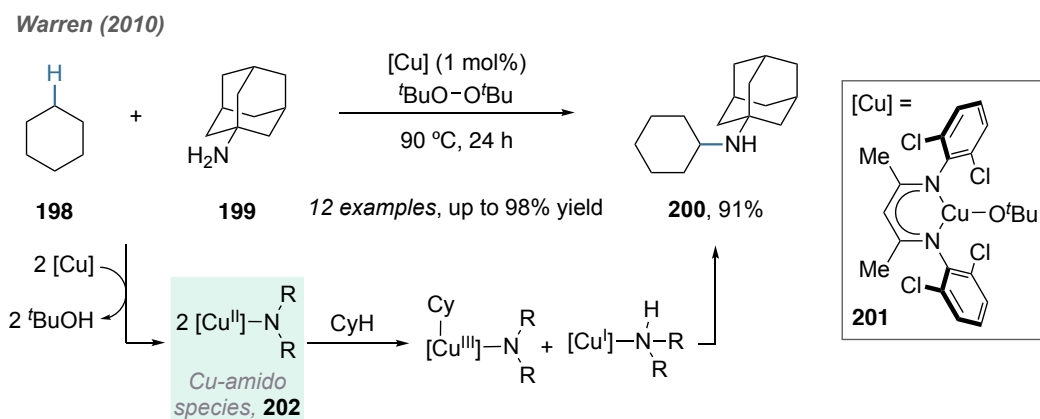
and good enantioselectivities for the sultam products **194** (up to 90% e.e.), the scope remained limited. In the same year, Arnold reported the directed evolution of an iron-containing enzymatic catalyst based on cytochrome P450 monooxygenase **195** for the enantioselective amination of benzylic C–H bonds (**196**) (Scheme 47b)<sup>243</sup>. Evolution of the protein through increasingly challenging reactivities enabled the stepwise growth of promiscuous activity, eventually leading to a function that the wild-type iron cofactor could not perform naturally. Although yields of the benzylamine products **197** varied widely (up to 86%) the general level of enantioselectivity was excellent (up to >99% e.e.), often with high turnover (up to 1,300 TON).



**Scheme 47** | (a) Biocatalytic intramolecular C–H amination. (b) CYP411-Catalyzed intermolecular C–H amination

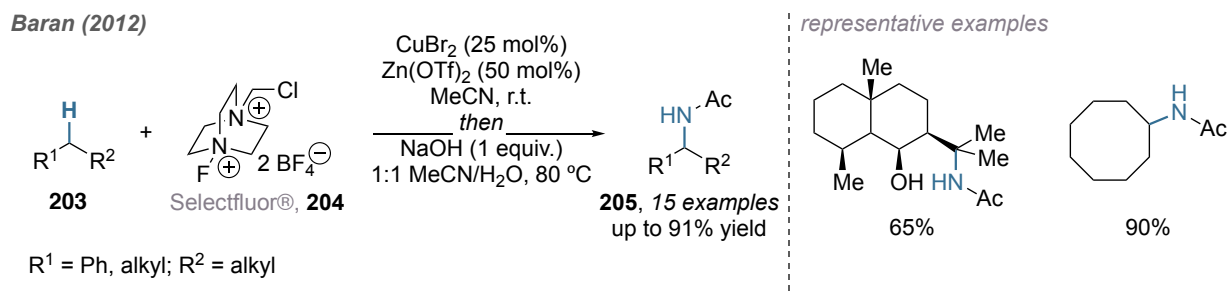
### 1.3.2 Metalloradical amination

Although metallonitrene insertion is widely considered to be the state-of-the-art for C–H amination reactions, multiple metal-catalyzed amination methodologies have evolved from the Kharasch-Sosnovsky reaction<sup>244,245</sup>, employing a combination of amine based oxidants such as NFSI<sup>246</sup> and peroxycarbamtes<sup>247</sup> with a copper-based catalyst. Importantly, in contrast to the insertion of nitrenes, both unactivated primary alkyl and secondary amines can be used, thus greatly expanding the scope of this transformation. A seminal report by Warren in 2010 demonstrated that a catalytic  $\beta$ -diketiminato dicopper species **201** in concert with di-*tert*-butylperoxide and simple primary and secondary alkylamines **199** could generate a reactive Cu–amido species **202** capable of reacting with simple hydrocarbons **198** (e.g. cyclohexane; BDE ca. 97 kcal/mol) (Scheme 48)<sup>248</sup>. The scope was subsequently extended from the generation of secondary alkylamines **200** to primary and secondary anilines; however, electron-rich substrates typically suffered from oxidative degradation, forming the corresponding diazene<sup>249</sup>.



Scheme 48 | Metalloradical based C–H amination of alkylamines

In 2012, Baran reported an intermolecular Ritter-type amination of unactivated C–H bonds<sup>250</sup>. Utilizing a combination of  $\text{CuBr}_2$ , Selectfluor® **204** and acetonitrile, several terpene-derived and simple hydrocarbon scaffolds **203** were successfully aminated under mild conditions in moderate to good yields, as well as on a gram scale (up to 91% yield) (Scheme 49). The authors hypothesized that oxidation of the  $\text{Cu}^{\text{II}}$ -species affords a highly reactive  $\text{Cu}^{\text{III}}$ -intermediate that is capable of hydrogen atom abstraction; oxidation of the radical to the carbocation and trapping with acetonitrile affords the aminated product **205**.

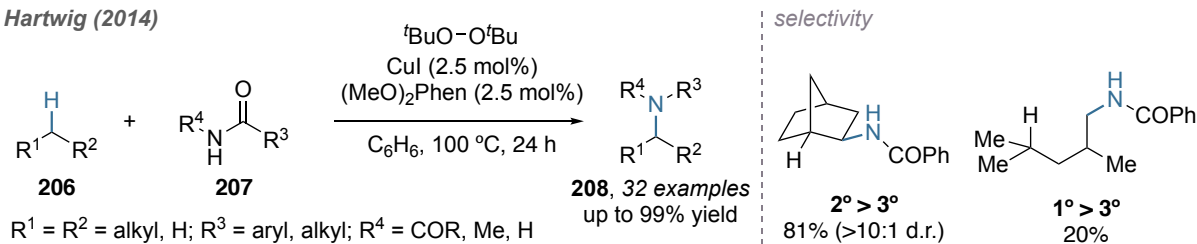


Scheme 49 | Cu-catalyzed intermolecular Ritter-type C–H amination

In 2014, Hartwig detailed a rare example of Cu-catalyzed intermolecular amidation and imidation (**207**) of unactivated alkanes **206** (Scheme 50)<sup>251</sup>. Remarkably, the combination of  $\text{CuI}$  and a  $(\text{MeO})_2\text{Phen}$  ligand with di-*tert*-butylperoxide resulted in the preferential amination of both  $2^\circ$  and  $1^\circ$  C–H bonds in the presence of  $3^\circ$  sites. The authors propose that this unusual selectivity is caused by steric clashing between the carbon centred radical and the phen-ligated  $\text{Cu}^{\text{II}}$ –amido species prior to reductive elimination. The scope of the reaction proved extremely general, tolerating an array of amides, phthalimides, oxazolidinones and sulfonamides in moderate to good yield. Furthermore, good yields and selectivities of the amine products **208** were obtained with simple hydrocarbons bearing multiple potentially reactive sites.



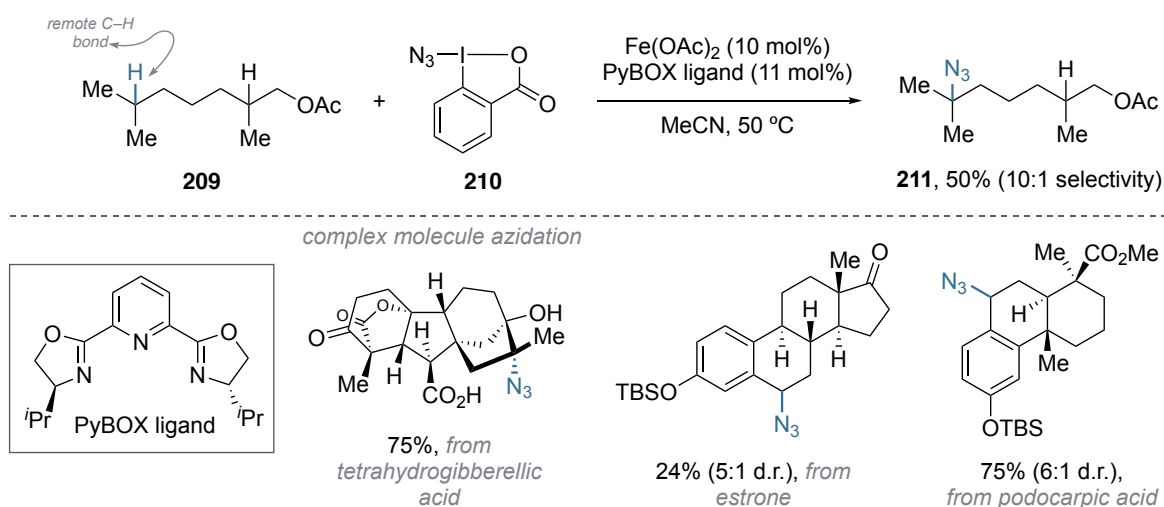
Hartwig (2014)



Scheme 50 | Intermolecular Cu-catalyzed C-H amidation

In 2015, Hartwig described a seminal Fe-catalyzed azidation of tertiary C-H bonds using a cyclic azidobenziodoxole reagent **210** (Scheme 51)<sup>252</sup>. The simple combination of  $\text{Fe}(\text{OAc})_2$  and PyBOX ligand resulted in a catalyst system that offered remarkably high levels of selectivity for remote, electron-rich C-H bonds in a variety of complex molecules **209**. Although often moderately yielding, the mild reaction conditions and superb functional group compatibility lends the protocol towards applications in late-stage functionalization<sup>253</sup>. Moreover, the versatility of the azide-substituted products **211** for further functional group manipulation beyond reduction to the primary amine is invaluable.

Hartwig (2015)



Scheme 51 | Fe-catalyzed intermolecular C-H azidation

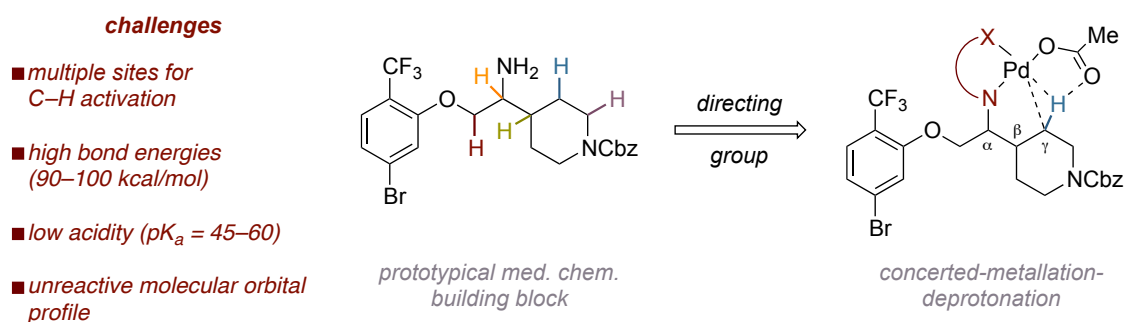
### 1.3.3 C-H bond activation via cyclometallation

Notwithstanding recent innovations in metallonitrene insertion and hydrogen atom abstraction chemistry, these technologies are fundamentally restricted as a result of their limited and oftentimes difficult to control selectivity. While important work has been achieved in high-valent metal Shilov-type amine  $\text{C}(sp^3)\text{-H}$  functionalization<sup>254,255</sup>, significant developments have been made in low-valent transition metal mediated processes; one whereby cleavage of the desired C-H bond typically occurs



via concerted metallation-deprotonation (CMD) mechanism<sup>256</sup>. While this type of reaction has proven particularly effective for the functionalization of aromatic C(sp<sup>2</sup>)-H bonds<sup>257</sup>, the cleavage of C(sp<sup>3</sup>)-H bonds presents an extra degree of complexity due to multiple degrees of freedom exhibited in aliphatic systems, as well an absence of available low lying orbitals through which to engage the metal<sup>258</sup>. These problems are further exemplified by the ubiquity of C(sp<sup>3</sup>)-H bonds in nature, rendering selectivity amongst the most prominent challenges in the development of catalytic processes.

*Transition metal catalyzed C(sp<sup>3</sup>)-H activation of alkyl amines*



**Scheme 52** | Overview of transition metal catalyzed C-H activation

Arguably, the most successful approach to dealing with the aforementioned issues has been through the use of directing groups; Lewis basic moieties that can coordinate to the metal centre and hold it proximal to a specific C(sp<sup>3</sup>)-H bond (Scheme 52)<sup>259</sup>. Subsequent C-H activation is able to proceed via a cyclometallation pathway, typically 5- or 6-membered, lowering the overall activation energy<sup>260</sup>. In general, the activation of methyl C(sp<sup>3</sup>)-H bonds is more facile than the corresponding methylene bonds due to increased sterics around the cyclopalladation transition state, offering complementarity to metallonitrene insertion<sup>261</sup>. Despite this, transition metal catalyzed C(sp<sup>3</sup>)-H amination remains surprisingly underexplored – primarily due to the kinetic instability of metal-amido species resulting in deleterious  $\beta$ -hydride elimination<sup>195</sup>. Although important advances have been made by Yu (W.-Y.)<sup>262</sup>, Chang<sup>263</sup>, and Yu (J.-Q.)<sup>264</sup> using Pd and Ir catalysts, these processes are predominantly limited to the activation of methyl and benzylic C(sp<sup>3</sup>)-H bonds. Recent pioneering work by Bergman and Ellman<sup>265</sup>, Shi<sup>266–268</sup>, Huang<sup>269</sup>, Cramer<sup>270,271</sup> and Miura<sup>272</sup>, amongst others<sup>273</sup>, have seen the development of transition metal catalyzed C-H bond addition to imines. In contrast to the traditional addition of organometallic reagents to imine derivatives<sup>274</sup>, the activation of C-H bonds and their addition to imines is both more atom-economical and displays greater functional group tolerance. Despite notable advances, especially recent progress in the development of asymmetric transformations and annulations<sup>271,275–277</sup>, this strategy currently relies upon fixed pyridine based directing groups either for C(sp<sup>2</sup>)-H or benzylic C(sp<sup>3</sup>)-H activation, and

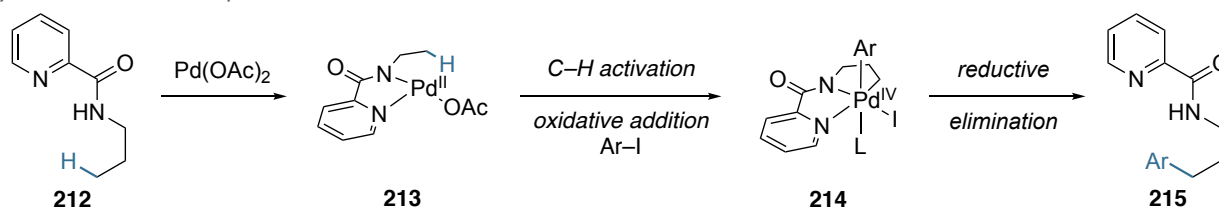
to date there are no examples of unactivated aliphatic C(sp<sup>3</sup>)-H bond addition to imines. On the other hand, the synthetic versatility of alkylamines themselves has resulted in the development of numerous strategies for transition metal catalyzed amine directed C(sp<sup>3</sup>)-H functionalization.

#### 1.3.4 Auxiliary controlled C-H functionalization

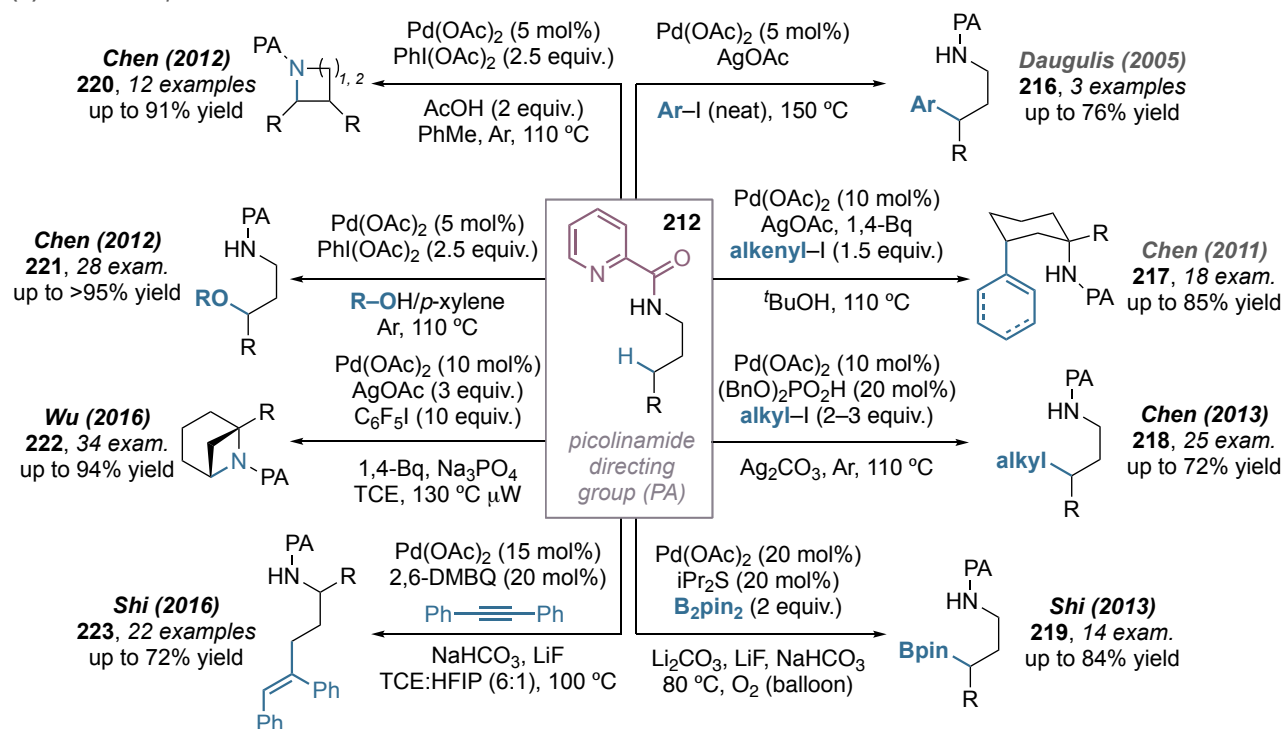
Seminal work by Daugulis in 2005 firmly cemented the picolinamide (PA) directing group into the arsenal of modern synthetic organic chemists. Primary amines bearing a PA group **212** were shown to undergo  $\gamma$ -C(sp<sup>3</sup>)-H arylation via a 5-membered ring palladacycle (Scheme 53a)<sup>278</sup>. Moreover, methylene C(sp<sup>3</sup>)-H bonds could also be arylated (**216**) in the absence of a suitable primary counterpart. The authors propose that bidentate coordination of both the amide and pyridine **213** enables facile  $\gamma$ -C(sp<sup>3</sup>)-H bond activation, generating a 5,5-fused palladacycle. Subsequent oxidative addition of the aryl iodide yields a Pd<sup>IV</sup>-intermediate **214** that affords the desired product **215** upon reductive elimination. Further reports by Chen<sup>279</sup>, Wang<sup>280</sup> and Zhao<sup>281</sup> expanded the scope of the transformation to include aryl and alkenyl iodides (**217**) under more mild conditions (Scheme 53b). Despite the proclivity of the PA group, a noted difficulty associated with its use was cleavage of the auxiliary following C-H functionalization. The design of a tailored PA auxiliary bearing a tethered protected alcohol **224** by Chen enabled cleavage under mild conditions, suitable for the formal synthesis of (+)-obafluorin (Scheme 53c)<sup>279</sup>. Recently, Chen reported the enantioselective PA directed benzylic C(sp<sup>3</sup>)-H arylation of phenpropylamines **225**, furnishing chiral diaryl amines **226**, in good yields and enantioselectivities (up to 97% yield, up to 97% e.e.) (Scheme 53d)<sup>282</sup>. The authors propose that the combination of BINOL phosphate ligand and caesium carbonate, generating a caesium phosphate complex **227**, may be involved in the stereodetermining C-H palladation step.

Such as the versatility of the PA group, Chen, Shi and Shi have developed protocols for alkylation using simple alkyl iodides (**218**)<sup>283</sup>, borylation (**219**)<sup>284</sup>, and  $\delta$ -alkenylation (**223**)<sup>285</sup> using simple alkynes via migratory insertion into a 6-membered palladacycle (Scheme 53b). Concurrently in 2012, Daugulis<sup>286</sup> and Chen<sup>287</sup> revealed the intramolecular C(sp<sup>3</sup>)-H amination of PA-protected amines using a PIDA oxidant to obtain pyrrolidines and azetidines **220** in good yields and respectable diastereoselectivities. A Pd<sup>II</sup>/Pd<sup>IV</sup> catalytic cycle was proposed by the authors whereby following C(sp<sup>3</sup>)-H activation, oxidation to Pd<sup>IV</sup> facilitates C-N bond forming reductive elimination. Later work by Wu expanded the scope to include polycyclic azetidines and pyrrolidines **222**<sup>288</sup>.

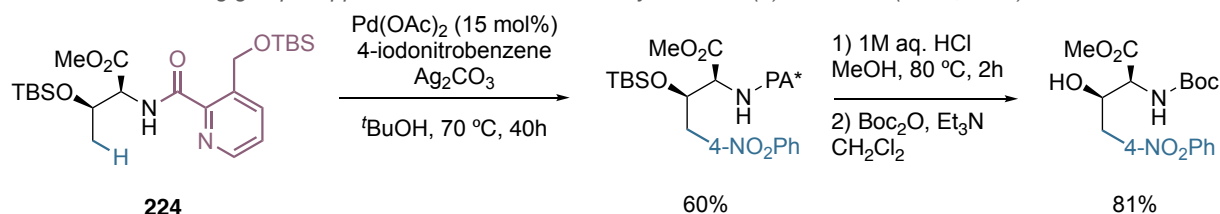
## (a) basic mechanism for picolinamide directed C–H functionalization



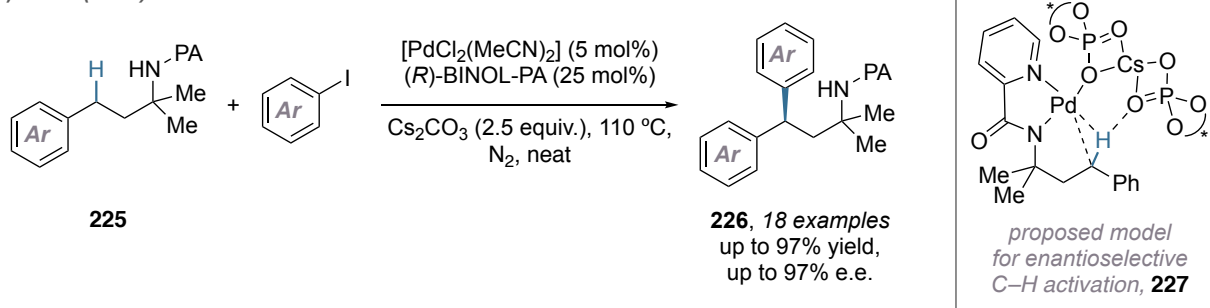
## (b) overview of picolinamide directed C–H functionalization reactions



## (c) modified PA\* directing group – application towards the formal synthesis of (+)-obafluorin (Chen, 2011)



## (d) Chen (2016)

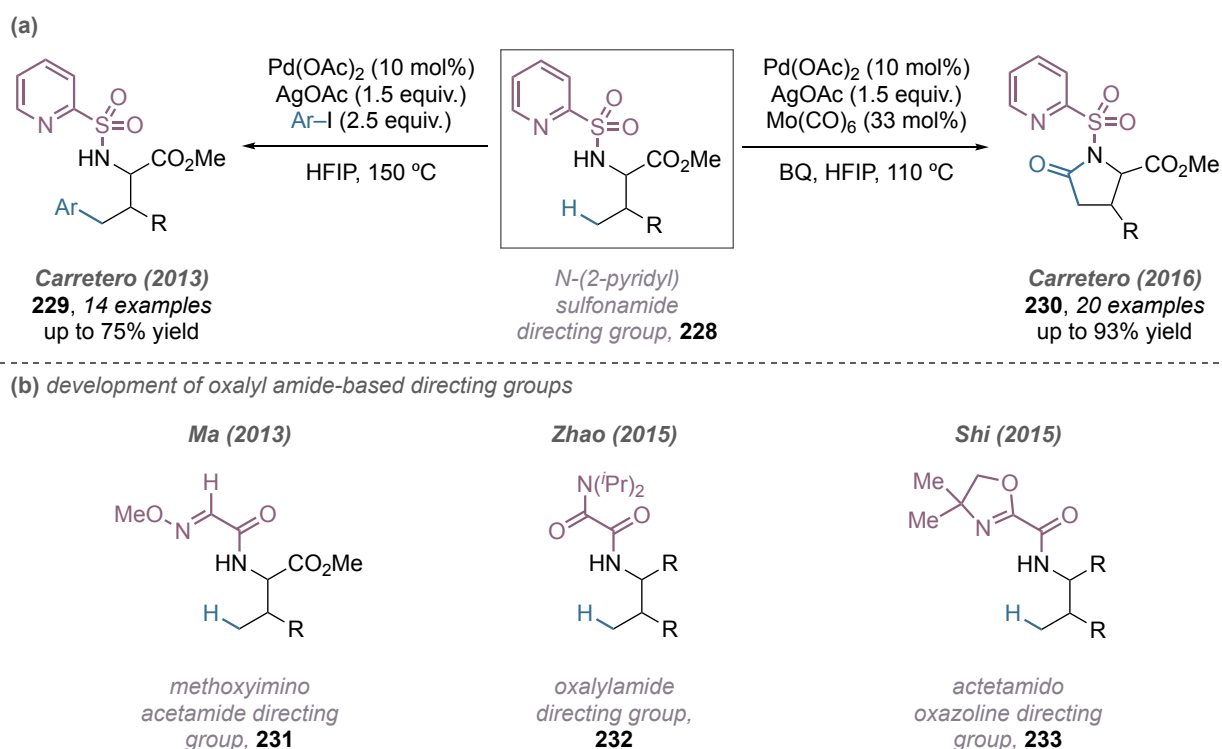


Scheme 53 | (a) General mechanism for PA directed C–H activation. (b) Overview of transformations. (c) Modified PA directing group. (d) Asymmetric PA directed C–H activation

Although the nature of C–N vs. C–O bond reductive elimination is not fully understood, it is believed that torsional strain within the in-plane C–N–N–Pd<sup>IV</sup> species is crucial for C–N bond

formation. As such, Chen reported careful modification of the reaction conditions through addition of an alcohol could lead to the corresponding alkoxyated products **221** selectively in good yields<sup>289</sup>.

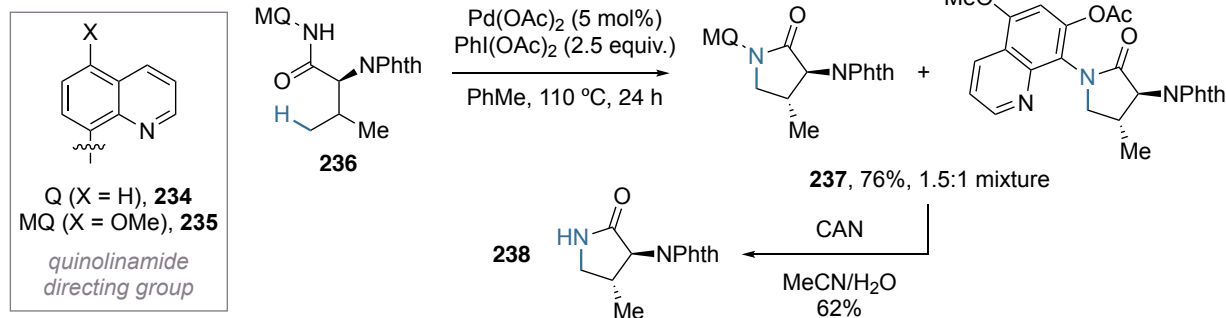
In 2013, Carretero described the isostructural *N*-(2-pyridyl)sulfonyl group **228** as an auxiliary for Pd-catalyzed intermolecular  $\gamma$ -C(*sp*<sup>3</sup>)-H arylation, delivering protected aryl amines **229**, in good yields (Scheme 54a)<sup>290,291</sup>. This synthetically versatile directing group can be readily introduced to the parent amine and removed under mild conditions in good yield using zinc powder. In 2016, the authors extended the scope to include the carbonylation of *N*-(2-pyridyl)sulfonyl amides to give pyrrolidones **230** in good yields and diastereoselectivities (Scheme 54a)<sup>292</sup>. Alongside the development of pyridine-based directing groups, Zhao<sup>293–295</sup>, Ma<sup>296</sup> and Shi<sup>297</sup> pioneered the use of oxalyl amide-derived auxiliaries for C(*sp*<sup>3</sup>)-H activation, leading to successful strategies for the carbonylation, acetoxylation and arylation of *N,N*-diisopropyl oxalyl amides **232**, the arylation of 2-methoxyiminoacetamides **231**, and the arylation of acetamidooxazolines **233** (Scheme 54b).



**Scheme 54** | (a) Sulfonylpyridine based directing group C-H functionalization. (b) Oxalyl amide based directing groups

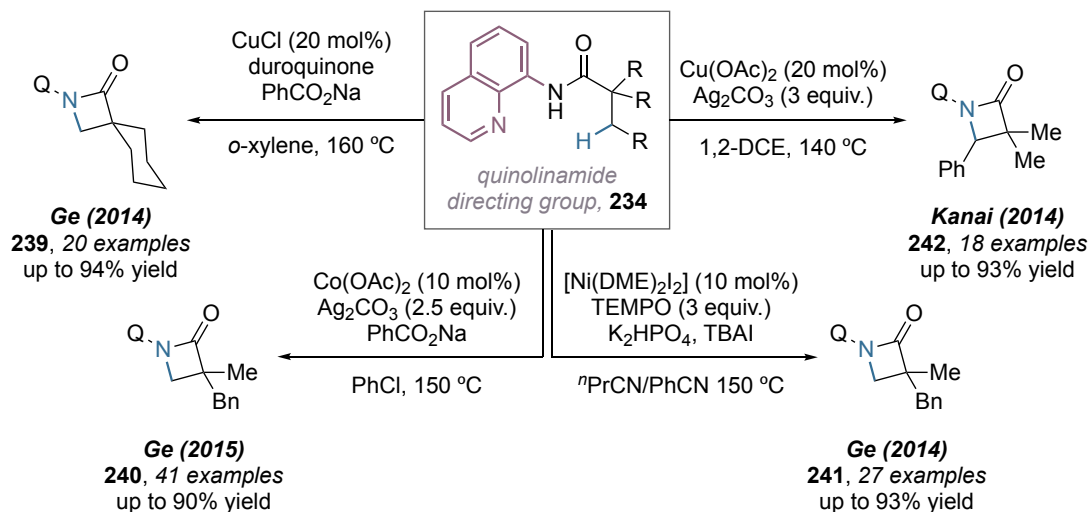
In addition to the elaboration of the PA auxiliary, Daugulis further pioneered the use of 8-aminoquinoline (Q) **234** as an efficient bidentate auxiliary<sup>278,298</sup>. In 2013, Chen disclosed the Q-directed Pd-catalyzed intramolecular activation  $\gamma$ -C(*sp*<sup>3</sup>)-H bonds (**236**) to form pyrrolidines **237** in good yields and high diastereoselectivities (Scheme 55)<sup>299</sup>. Notably, the use of 8-amino-5-methoxyquinoline as an auxiliary (MQ) **235** enabled facile deprotection to the free (*NH*)-lactam **238** using CAN under mild conditions.

Chen (2013)



Scheme 55 | Quinolinamide directed C–H activation and deprotection

Subsequent significant reports highlighted the versatility of the Q auxiliary not only in Pd-catalyzed C(sp<sup>3</sup>)–H amination, but also for use in first-row metal catalyzed processes (Scheme 56). In 2014, Kanai (**242**)<sup>300</sup> and Ge (**239**)<sup>301</sup> independently reported the Cu-catalyzed intramolecular oxidative C(sp<sup>3</sup>)–H amination of quinolinamides to give azetidinones and pyrrolidones in good yields and high selectivities. Moreover, Ge reported the intramolecular Ni-catalyzed intramolecular oxidative C(sp<sup>3</sup>)–H amination (**241**) in good yields<sup>302</sup>. Unlike Cu-catalyzed processes, activation occurred primarily at the β-methyl position leaving benzylic positions intact. Recent work by Ge<sup>303</sup>, Zhang<sup>304</sup> and Gaunt<sup>305</sup> has shown that the amides containing Q-directing group are amenable to Co-catalyzed oxidative amination **240**, alkenylation and carbonylation. Importantly, Ge found that γ-benzylic C–H bonds were selectively activated in the presence of β-methyl groups – the opposite pattern of selectivity to Kanai's Cu-catalyzed process (**242**).

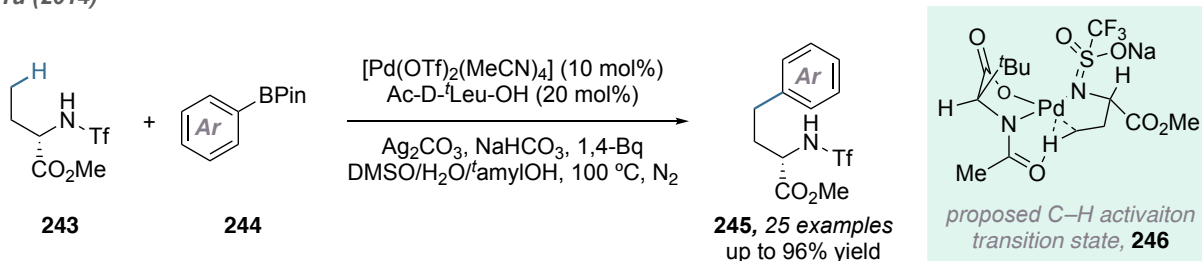


Scheme 56 | Overview of Q-directed C–H activation transformations

The use of strong σ-donor/π-acceptor bidentate directing groups has paved the way in the development of new transition metal catalyzed C–H functionalization technologies. However, one potential disadvantage of this approach is the necessity for extra, often harsh, synthetic steps required for installation and removal. Additionally, the thermodynamically stable cyclometallated species can

be less prone towards further functionalization, therefore restricting the range of nucleophiles and electrophiles with which they can react. Along these lines, cyclometallation of weakly-coordinating directing groups (such as ketones, amides and carboxylic acids) offers distinct advantages; however, the intermediate palladacycles are far less stable and hence less studied<sup>306</sup>. In 2014, Yu reported the Pd-catalyzed C(*sp*<sup>3</sup>)-H functionalization of triflamides **243** – a weakly-coordinating monodentate auxiliary (Scheme 57)<sup>307</sup>. Utilizing both electron-rich and electron-poor aryl boronic esters **244**, the  $\gamma$ -aryl substituted aliphatic amine products **245** could be accessed in good yields. Mechanistic studies by Houk and Yu elucidated that the mono-protected amino acid (MPAA) ligand was critical to the success of the reaction; the dianionic amidate **247** participates in an intramolecular CMD process leading both to higher reactivity and selectivity<sup>308</sup>.

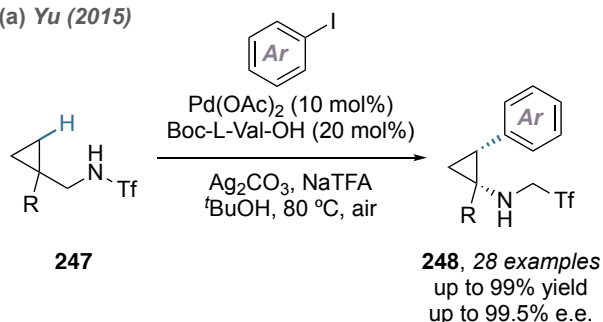
Yu (2014)



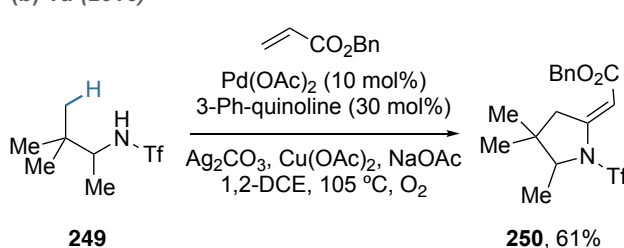
Scheme 57 | Asymmetric triflamide directed C–H arylation

The synergistic relationship between Pd and MPAA ligands led to the ensuing development of a highly enantioselective C(*sp*<sup>3</sup>)-H arylation of Tf-cyclopropylmethylamines **247** (Scheme 58a)<sup>309</sup>. Excellent yields and enantioselectivities were observed (up to 99% yield, up to >99.5% e.e.) for the resulting *cis*-arylated products **248** via a proposed Pd<sup>II</sup>/Pd<sup>IV</sup> manifold. Subsequent advancements by Yu using quinoline-derived ligands facilitated the development of Tf- and Ns-protected amine **249** alkenylation protocols, furnishing pyrrolidines **250** in good yields (Scheme 58b)<sup>310</sup>.

(a) Yu (2015)



(b) Yu (2016)

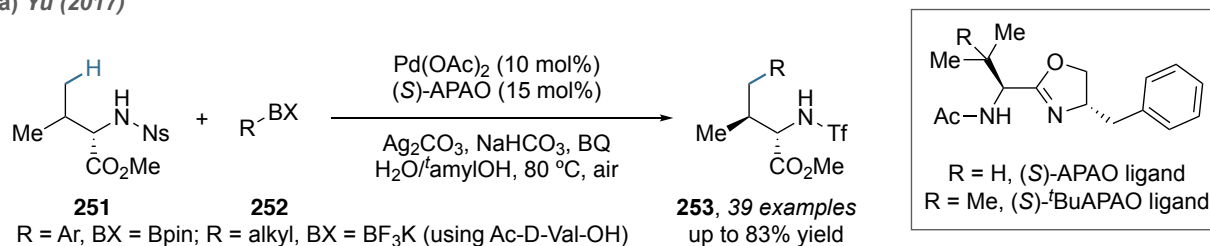


Scheme 58 | (a) Asymmetric triflamide directed C–H arylation. (b) C–H Alkenylation/cyclization

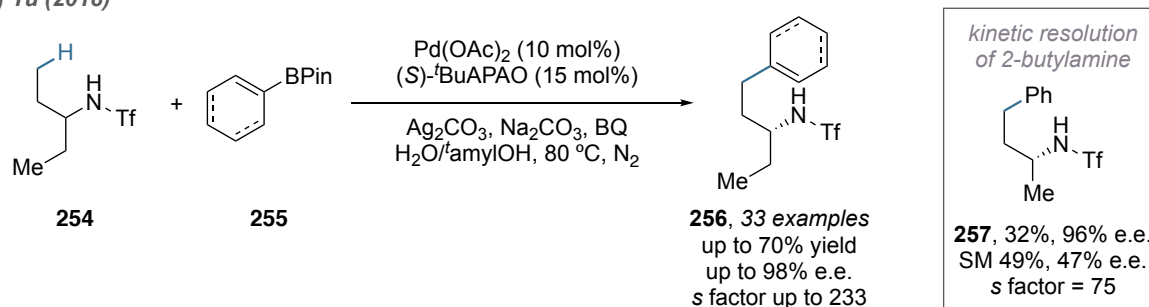
Further ligand development by Yu led to the implementation of an *N*-acetyl aminomethyloxazoline-derived ligand (APAO) for the  $\gamma$ -C(*sp*<sup>3</sup>)-H arylation of Ns-protected amino acids **251** in good yields and excellent diastereoselectivities (Scheme 59a)<sup>311</sup>. The parent *N*-acetyl valine ligand was found to be effective for the alkylation of Ns-protected amino acids using Molander-type potassium

trifluoroborate salts **252** in good yields with similarly high diastereoselectivities. Despite the practicality of the process for the synthesis of difficult to access non-natural amino acids, the reaction often affords mixtures of mono- and di-arylated products **253**. Recently, Yu disclosed the Pd-catalyzed enantioselective desymmetrization/kinetic resolution of  $\alpha$ -branched Tf-protected alkylamines **254** in good yields and excellent enantioselectivities (Scheme 59b)<sup>312</sup>. Chiral APAO ligands derived from *tert*-leucine facilitated both the arylation and vinylation (**256**) from a diverse range of boronic esters **255**. Notably, impressive enantioselectivities could be achieved for challenging substrates including 2-butylamine, generating 1-methyl-3-phenylpropylamine **257** (96% e.e.), where steric differentiation between the methyl group and hydrogen is small.

## (a) Yu (2017)



## (b) Yu (2018)



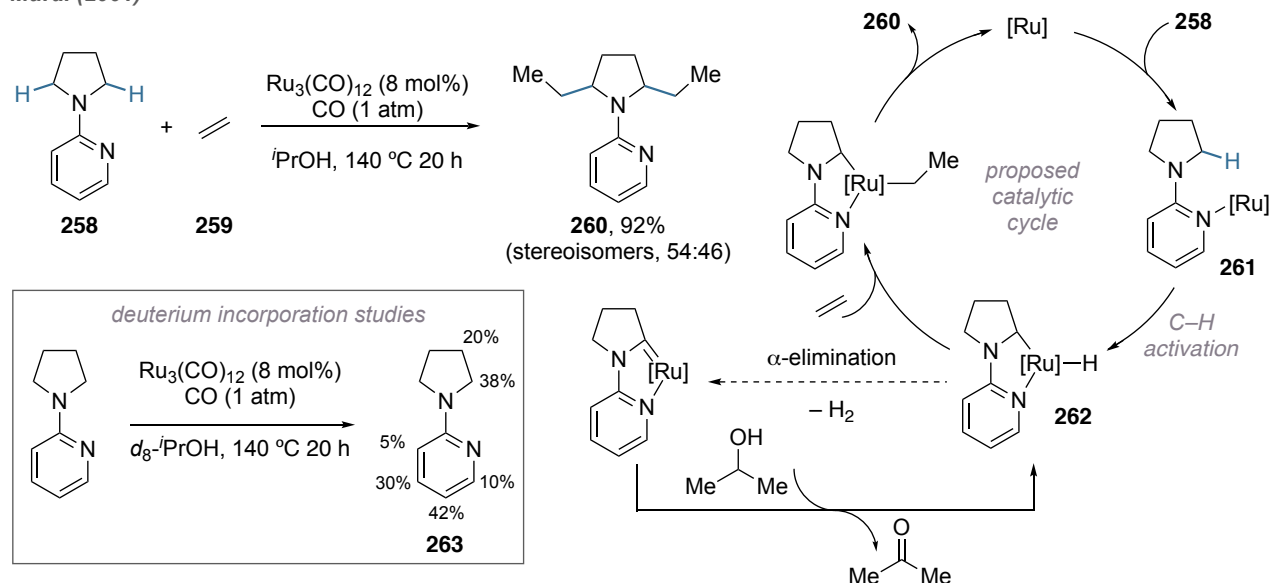
**Scheme 59** | (a) Nosylamide directed C-H arylation and alkylation. (b) Asymmetric C-H arylation kinetic resolution

Despite the plethora of  $\gamma$ - and  $\delta$ -C(*sp*<sup>3</sup>)-H functionalization methodologies developed over the last two decades, the analogous functionalization of  $\alpha$ - and  $\beta$ -positions has been comparatively underexplored<sup>313</sup>. Although extensive work has been accomplished by Hartwig and others using early transition metal catalysts (e.g. Ta, Nb, Ti, Zr) for the hydroaminoalkylation of olefins with dialkylamines<sup>314–318</sup>, early studies by Jun<sup>319</sup> and Murai<sup>320</sup> described the Ru<sub>3</sub>(CO)<sub>12</sub>-catalyzed  $\alpha$ -coupling of alkylamines **258** with simple alkenes **259** in moderate to good yield, albeit with mixtures of mono- and di-functionalized product **260** (Scheme 60). Although a large range of directing groups were explored (carbamates, amides, amidines), the superior chelation ability of the *sp*<sup>2</sup> nitrogen in pyridine was required to displace the strongly bound CO ligands of the catalyst **261**. Alcohol solvents were found to be critical to the success of the reaction, probably due to their regenerative hydrogen-donating ability in the case of deleterious  $\alpha$ -elimination of the intermediate Rh-H species **262**. Although a range of potential mechanisms were proposed by the authors, including direct



oxidative insertion in to the C–H bond, deuterium labelling studies revealed incorporation at all positions **263**, indicating facile non-selective C–H bond cleavage.

Murai (2001)



**Scheme 60** | Pyridine directed  $\alpha$ -C–H alkenylation of alkylamines

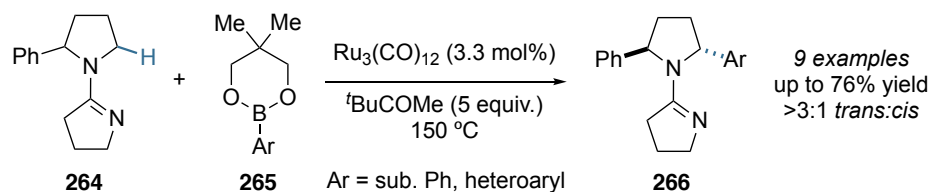
In 2006, Sames reported the C–H arylation of pyrrolidines and piperidines using an amidine directing group **264**, easily installed by the reaction between a secondary amine and 2-methoxypyrroline (Scheme 61a)<sup>321</sup>. Using the same  $\text{Ru}_3(\text{CO})_{12}$  catalyst and an aryl boronic ester **265**, moderate to good yields of the arylated product **266** could be achieved alongside reasonable *trans/cis* ratios of the di-substituted pyrrolidines. In 2010, Maes extended the scope to include the C-2 arylation of (2-pyridyl)piperidines **267** in good yield using aryl boronates (Scheme 61b)<sup>322</sup>. Importantly, the pyridyl-directing group could be removed in modest yield via a two-step hydrogenation-nucleophilic displacement protocol, liberating the free (NH)-piperidine **268**. Subsequent reports by Schnürch<sup>323</sup> and Ackermann<sup>324</sup> described the arylation of acyclic 2-(benzylamino)pyridines using aryl boronates and aryl halides in modest yields. In 2011, an interesting asymmetric  $\text{Ir}^{\text{I}}$ -catalyzed alkenylation of 2-(alkylamino)pyridines **269** with vinyl arenes **270** was reported by Shibata, furnishing the phenylpropylamine products **271** in good yields and good enantioselectivities (up to 89% yield, up to 90% e.e.) using a tolBINAP ligand (Scheme 61c)<sup>325</sup>.

Due to the challenges associated with over-alkylation, poor stereocontrol and synthetically restrictive auxiliaries, the widespread adoption of low-valent Ru-catalysts has been met with limited success. In 2014, Yu reported the  $\alpha$ -arylation of saturated azacycles and *N*-methyl secondary amines using catalytic  $\text{Pd}(\text{TFA})_2$  and aryl boronic acids under more synthetically amenable conditions<sup>326</sup>. Using a thioamide-directing group to modulate the electronics of the strained cyclopalladated intermediate, a

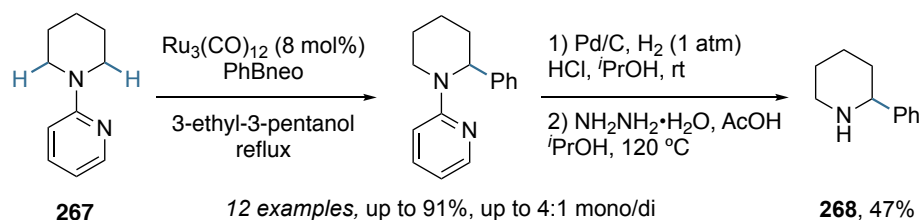


range of ring sizes could be accommodated as well as synthetically versatile aryl and heteroaryl boronic acids in good yields without competing di-arylation. Interestingly, the corresponding amide showed no activity.

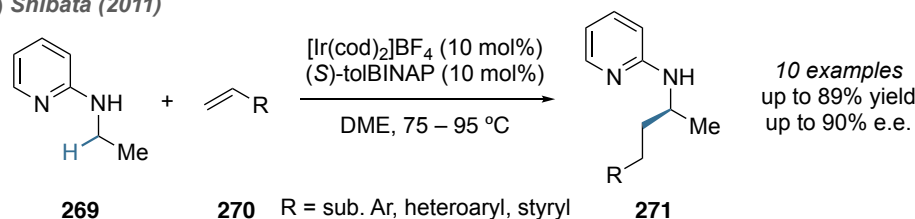
## (a) Sames (2006)



## (b) Maes (2010)



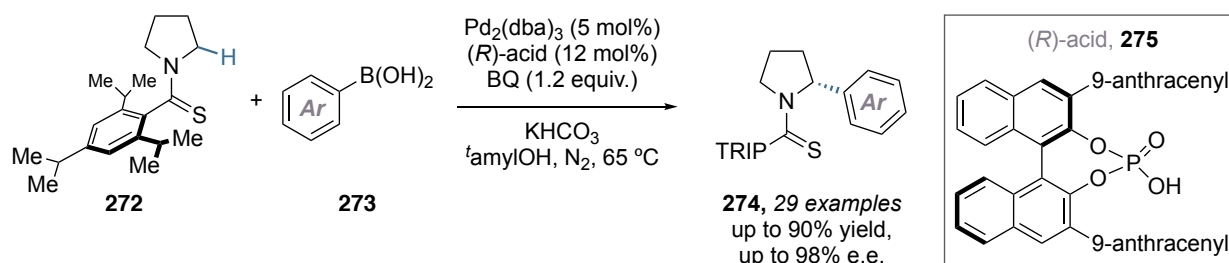
## (c) Shibata (2011)



**Scheme 61** | (a) Amidine directed  $\alpha$ -C–H arylation. (b) Pyridine directed  $\alpha$ -C–H arylation/deprotection. (c) Asymmetric acyclic benzyl C–H alkenylation

Subsequently, Yu described an elegant asymmetric protocol for the thioamide-directed arylation of azacycles **272** and dialkylamines using aryl boronic acids **273** (Scheme 62)<sup>327</sup>. Using a combination of a bulky 2,4,6-triisopropylphenylthioamide auxiliary and chiral anthracenyl-substituted BINOL phosphoric acid **275**, the resulting arylated heterocycles **274** could be accessed in good yields and high enantioselectivities (up to 90% yield, up to 98% e.e.).

## Yu (2017)

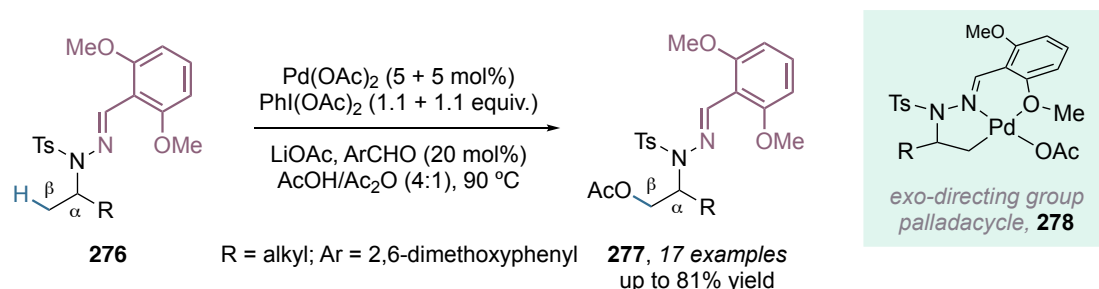


**Scheme 62** | Thioamide directed asymmetric C–H arylation

Predominantly, general procedures for  $\beta$ -amine functionalization have been less well-studied. In order to undergo  $\gamma$ -cyclopalladation at the  $\beta$ -position to the amine, the directing group would need to possess a stable Lewis basic site at the opposing  $\alpha$ -position, a substitution pattern not commonly

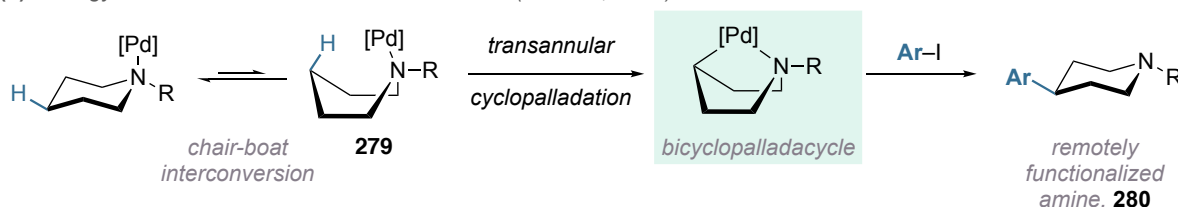
encountered in organic chemistry due to its reactivity. In 2016, Dong reported a hydrazone based *exo*-directing group strategy **276** (the term *exo* refers to the position of the  $\pi$ -bond after C–H metalation **278**<sup>328</sup>) for the Pd-catalyzed  $\beta$ -acetoxylation (**277**) and tosylation of alkylamines in moderate to good yields (Scheme 63)<sup>329</sup>. Due to the instability of the directing group towards hydrolysis and elimination, the parent aldehyde and nitrile were observed as significant impurities; therefore, additional aldehyde and acetic anhydride were employed as additives. Importantly, the hydrazone directing group could be cleaved in a ‘one-pot strategy’ in good yield using Zn directly added at the end of the reaction.

Dong (2016)

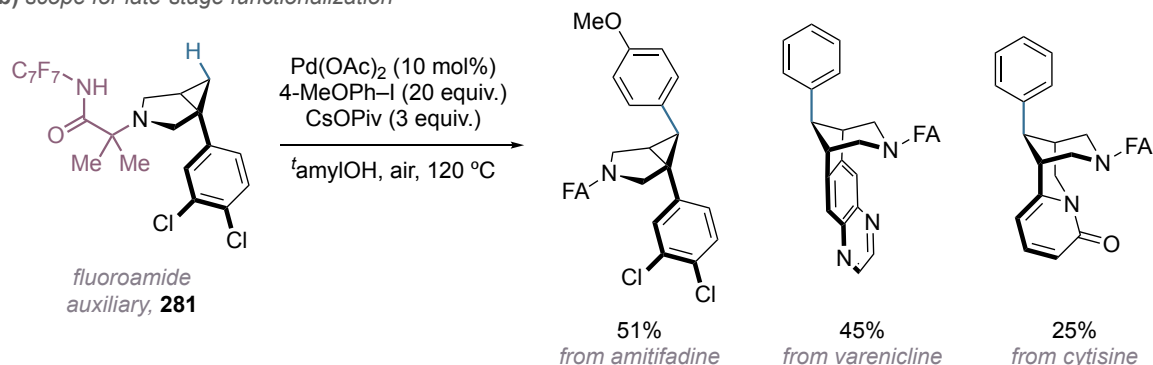
Scheme 63 | Hydrazone directed  $\beta$ -C–H acetoxylation of tosylamides

In 2016, Sanford reported the Pd-catalyzed transannular C–H functionalization of alicyclic amines, bringing otherwise remote C–H bonds close to the Pd-centre via the boat conformation **279** (Scheme 64a)<sup>330</sup>. Given the abundance of piperidine scaffolds amongst pharmaceuticals<sup>63</sup>, the application of this transformation towards late-stage functionalization proved particularly fruitful.

(a) strategy for remote transannular C–H activation (Sanford, 2016)



(b) scope for late-stage functionalization



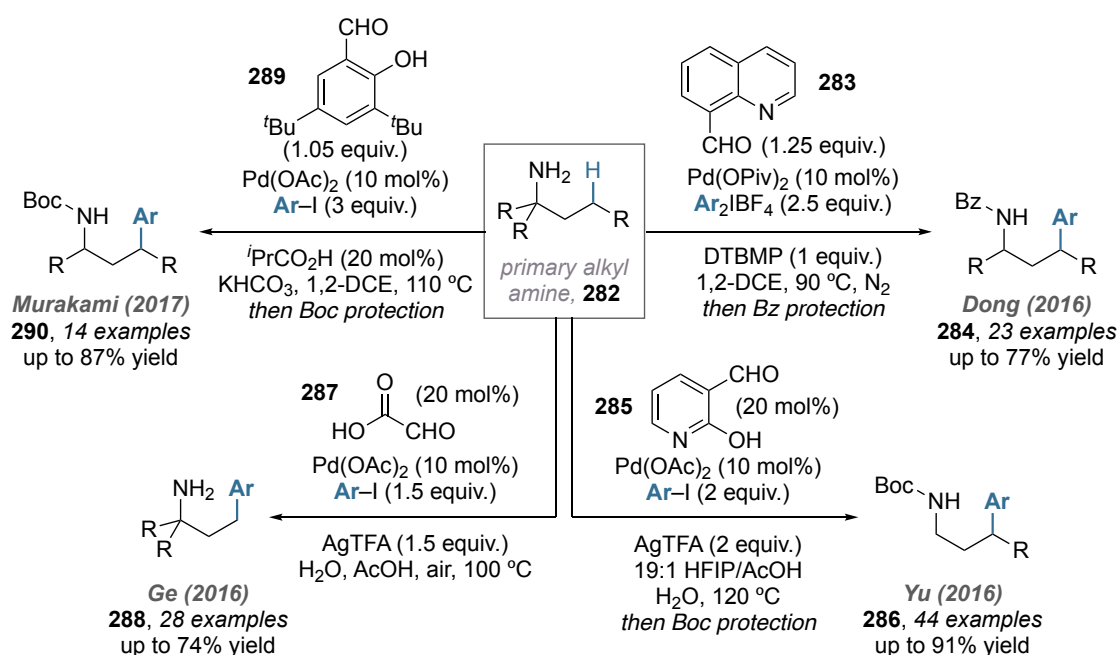
Scheme 64 | (a) Design plan for transannular C–H arylation. (b) Scope for late-stage functionalization

Utilizing a bespoke fluoroamide (FA) auxiliary **281**, fused aza-bicycles as well as piperidines could be arylated **280** in synthetically useful yields by a range of aryl- and heteroaryl iodides (Scheme 64b). Given the low equilibrium population of the boat conformation **279**, high temperatures (130 °C) were required; therefore, substituting AgOPiv for the non-oxidizing CsOPiv was vital in suppressing deleterious  $\alpha$ -oxidation. Recently, Sanford disclosed a second-generation Pd-catalyst system employing picoline and quinoline carboxylic acid additives, dramatically improving the catalyst turnover and enabling the arylation of previously incompatible tropane scaffolds<sup>331</sup>. Given that the auxiliary can be removed in good yield, albeit capriciously, the impressive scope, selectivity, and utility of this methodology has rendered it an important asset in the amine C–H functionalization toolkit.

### 1.3.5 Transient directing group assisted C–H functionalization

In spite of the important advances made in the field of directed amine C–H functionalization, the requisite installation and removal of these auxiliaries goes some way to reducing the overall efficiency of these processes. A more atom-economical concept would be the development of so-called transient directing groups (TDG) whereby the generation and removal of the auxiliary occurs *in-situ*, temporarily modifying existing native functionality within the molecule (Scheme 65). In 2016, Dong reported the use of super-stoichiometric 8-formylquinolinamide **283** as a transient directing group for the Pd-catalyzed  $\gamma$ -C–H arylation of primary alkylamines **282**<sup>332</sup>. Condensation of the  $\alpha$ -branched primary amine substrate and 8-formylquinolinamide afforded the corresponding *exo*-imine, which underwent arylation at both methyl and methylene C–H bonds with reactive Ar<sub>2</sub>IBF<sub>4</sub> salts in moderate to good yields (**284**), although diarylation was observed in certain cases. At the same time, Ge reported the  $\gamma$ -C–H arylation of primary alkylamines using catalytic quantities of glyoxylic acid **287** (20 mol%) as a directing group in moderate to good yields<sup>333</sup>. Coordination of the Pd-catalyst with the transiently generated  $\alpha$ -imino acid intermediate and subsequent C–H activation furnishes a 5-membered palladacycle intermediate. Oxidative addition of the aryl iodide to Pd<sup>IV</sup>, followed by reductive elimination and hydrolysis, leads to the product **288** and regeneration of glyoxylic acid. Importantly the use of  $\alpha$ -tertiary substituted alkylamines was crucial to the success of the reaction, as the corresponding  $\alpha$ -branched amines gave only trace product. Moreover, Yu subsequently reported that catalytic 2-hydroxynicotinaldehyde **285** could also be employed for the Pd-catalyzed  $\gamma$ -arylation of primary alkylamines using aryl- and heteroaryl iodides in good yields (**286**)<sup>334</sup>. In contrast to the reports by Dong and Ge, unbranched alkylamines such as propylamine could be arylated in good yields alongside an array of  $\alpha$ - and  $\beta$ -branched amine substrates,

undergoing both methyl and methylene activation. Additionally, the catalyst and directing group loading could be lowered to 2 and 4 mol% respectively without serious impact on the yield. Recently, 3,5-di-*tert*-butylsalicylaldehyde **289** was found to be another competent transient directing group for alkylamine C–H activation, although pre-condensation between the aldehyde and amine substrates, as well as hydrolysis, were carried out independent to the reaction<sup>335</sup>. A variety of aryl- and heteroaryl iodides were tolerated in good yields (**290**) for  $\alpha$ -branched alkylamines. Impressively, propylamine could be arylated in moderate yield via a pre-formed ketimine-derived transient directing group. Given the high efficiency and broad scope already achieved with this emerging technology, transient-directing-group-assisted amine C–H functionalization is a feat that will have doubtless implications across the synthetic community.

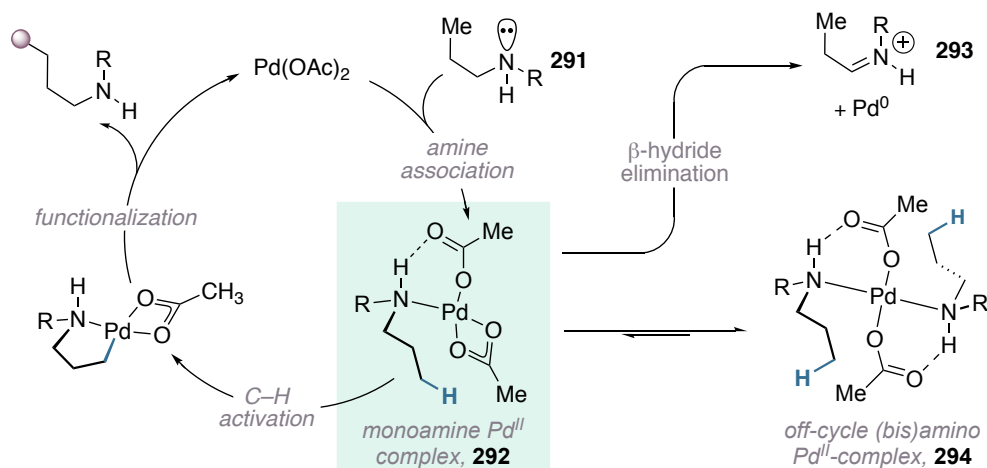


**Scheme 65** | Overview of transient directing group assisted C–H arylation of alkylamines

### 1.3.6 Free (NH)amine directed C–H functionalization

The recent growth in transient directing group-mediated C–H functionalization has enabled transformations previously thought impossible using transition metal catalysis. Nevertheless, the scope is currently limited to the arylation of primary alkylamines, not to mention the necessity for multiple additives or strict inert atmosphere conditions in order to achieve high conversion. Given these potential limitations, the development of methodologies able to functionalize alkylamines using the native coordinating ability of the nitrogen lone pair, would offer a considerable strategic advantage – especially for late-stage functionalization.

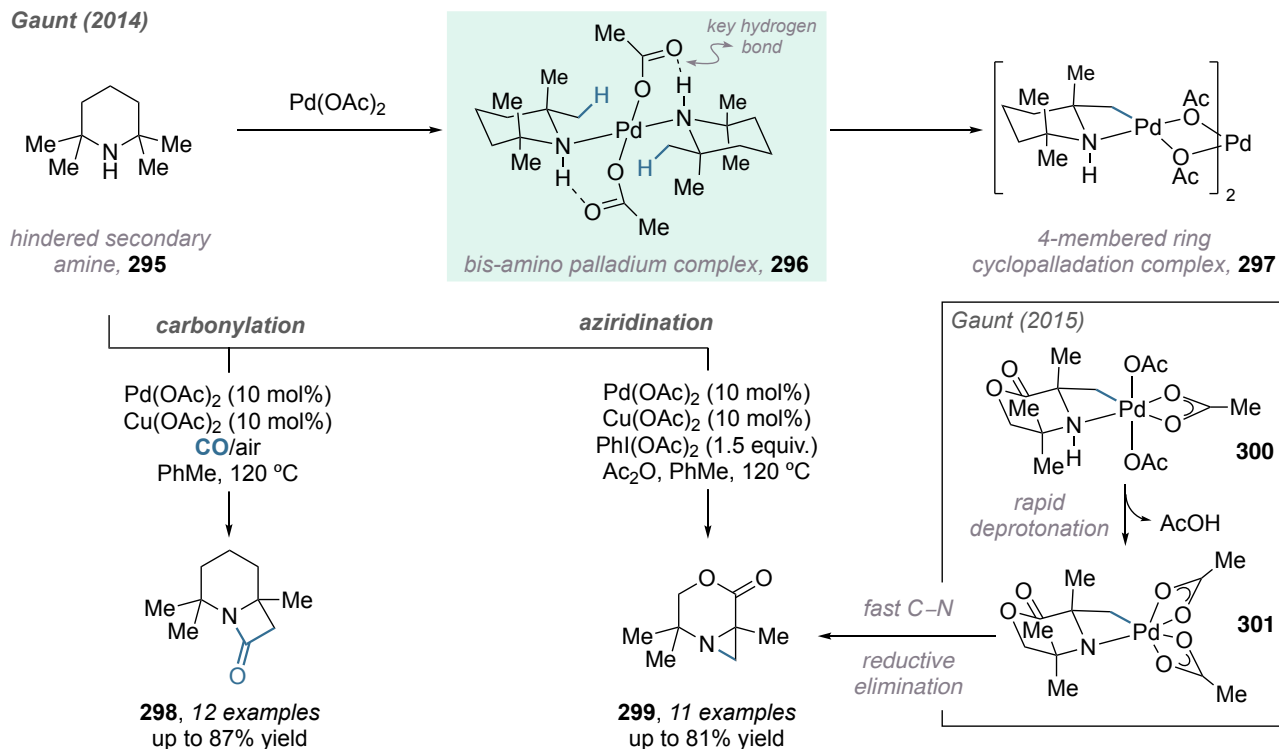
Despite the simplicity of this proposal, there are several factors that have impeded the use of native amines to direct C–H activation (Scheme 66). Unlike weakly-coordinating amides and sulfonamides, alkylamines **291** ligate strongly to transition metal centres **294**, thereby saturating vacant sites required for C–H activation to occur **292**<sup>336</sup>. Furthermore, the facile  $\beta$ -hydride elimination from Pd-bound alkylamines **293**, so exploited in cross-coupling chemistry, would need to be curtailed.



**Scheme 66** | General scheme for free(NH) amine directed C–H functionalization

In 2014, seminal work by Gaunt described the first catalytic Pd-catalyzed C–H activation of aliphatic amines to form strained nitrogen heterocycles (Scheme 67)<sup>337</sup>. By using 2,2,6,6-tetramethylpiperidine (TMP)-derived amines **295**, deleterious  $\beta$ -hydride elimination could be eliminated and the additional sterics around the nitrogen centre were able to facilitate the formation of the catalytically active *mono*-amine-Pd species, from the stable *bis*-amine complex **296**<sup>338,339</sup>.

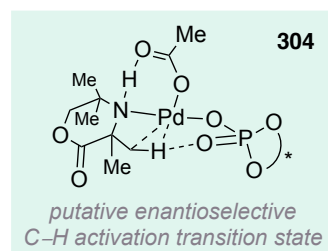
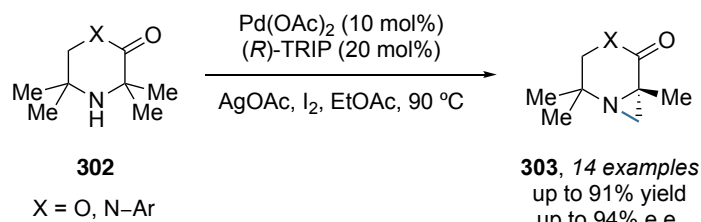
Gaunt (2014)



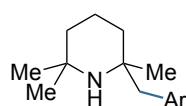
Scheme 67 | Hindered alkylamine directed C–H functionalization

Importantly, the combination of these factors led to a remarkably facile 4-membered cyclopalladation of the proximal methyl groups **297**, resulting in the development of catalytic carbonylation (**298**) and oxidative aziridination protocols (**299**). Importantly, such hindered products would be extremely challenging to make via existing methods. Interestingly, the morpholinone scaffold **302** proved crucial to the success of the oxidative aziridination; subsection of TMP to the same conditions led instead to acetoxylation. Recent mechanistic and computational studies into the oxidative aziridination have revealed that the addition of acetic acid significantly increases the rate of reaction by suppressing the formation of an off-cycle *bis*-amine Pd-complex **296**<sup>340</sup>. Importantly, rapid deprotonation of the amine bound cyclometallated  $\text{Pd}^{\text{IV}}$ -intermediate **300** gives rise to an Pd-amido species **301**, favouring C–N over C–O reductive elimination.

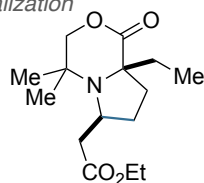
## (a) Gaunt (2017)



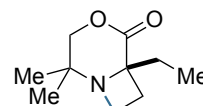
## (b) hindered amine directed C-H functionalization



**arylation (2015)**  
**305**, 23 examples  
up to 68% yield



**γ-alkenylation (2017)**  
**306**, 27 examples  
up to 93% yield

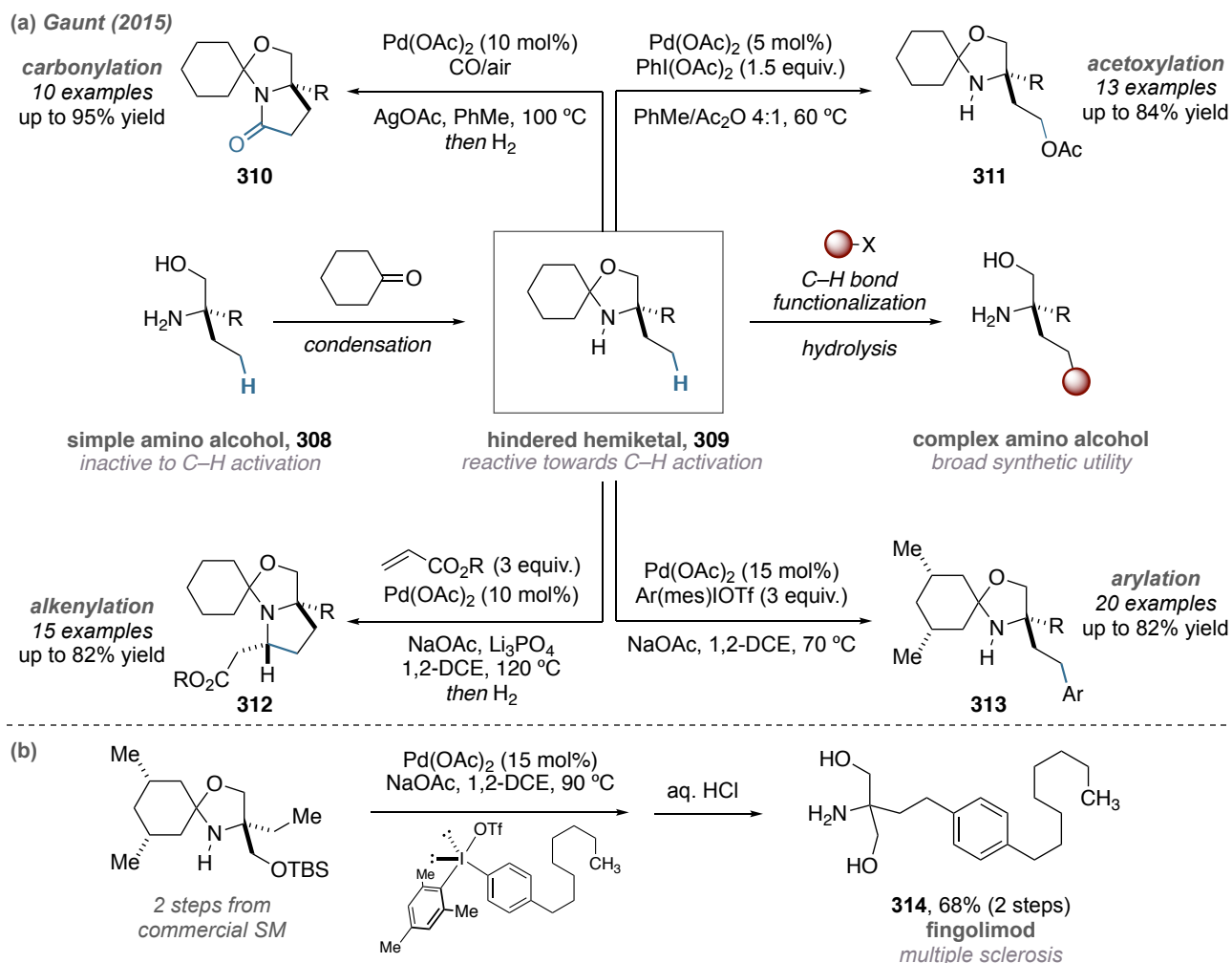


**aziridination (2018)**  
**307**, 23 examples  
up to 83% yield

**Scheme 68** | (a) Asymmetric C-H aziridination of alkylamines. (b) Scope of hindered amine functionalization

The identification of a key amine to acetate hydrogen bond **304** led to the development of an asymmetric Pd-catalyzed aziridination of tetrasubstituted morpholinones and piperazinones (**303**) in good yields and good enantioselectivities using a chiral TRIP phosphoric acid (up to 91% yield, up to 92% e.e.) (Scheme 68a)<sup>341</sup>. Based on this, a series of methodologies were developed including the β-arylation of TMP derivatives (**305**)<sup>342</sup> as well as the γ-alkenylation<sup>343</sup> and γ-C-H amination<sup>344</sup> of morpholinones to form unique fused pyrrolidine **306** and azetidine **307** scaffolds (Scheme 68b).

In 2015, Gaunt reported a steric tethering approach for the Pd-catalyzed C-H activation of primary amino alcohols **308** (Scheme 69a)<sup>345</sup>. By protecting an α-tertiary amino-alcohol moiety as a sterically encumbered hemiketal **309**, a range of high yielding transformations including carbonylation (**310**), acetoxylation (**311**), alkenylation (**312**) and arylation (**313**) could be readily performed. The presence of both a putative hydrogen bond to lock the conformation of the hemiketal in the correct geometry for cyclopalladation, as well as the steric repulsion for destabilizing the off-cycle *bis*-amino Pd complex, were attributed as the key factors responsible in achieving the C-H activation process. The applicability of this strategy was exemplified by the modular synthesis of four fingolimod analogues **314** in good yield, a key treatment for multiple sclerosis (Scheme 69b).



**Scheme 69** | (a) Steric tethering strategy for amino alcohol C–H functionalization. (b) Synthesis of fingolimod

A recent report by Shi described the  $\gamma$ -C( $sp^3$ )–H acetoxylation of  $\alpha$ -tertiary primary amines in moderate yields<sup>346</sup>. By modulating the concentration of free amine via protonation, the coordinating ability of the amine and hence the formation of an off-cycle *bis*-amino Pd complex can be attenuated. Irrespectively, the functional group tolerance is limited to remote positions to avoid further chelation, limiting its overall synthetic application.

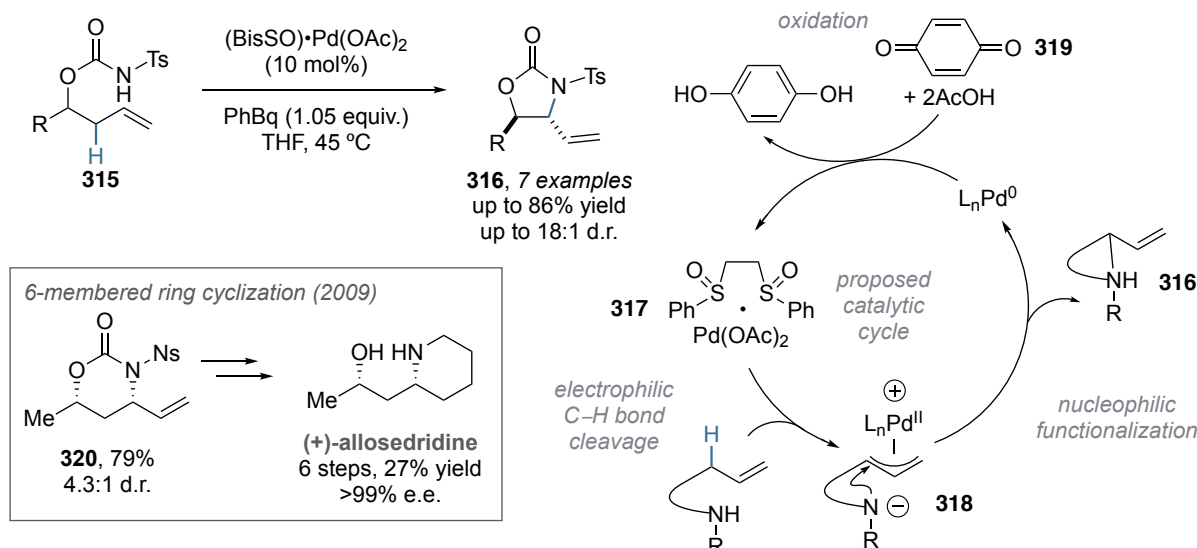
### 1.3.7 Allylic C–H amination

Over the last two decades, the related allylic C–H amination has dawned a new era for allylic substitution reactions. Whereas traditional allylic substitution relies upon a suitably displaced leaving group<sup>347</sup>, C–H activation offers a direct route to complex amine products from simple unfunctionalized hydrocarbons. The cornerstone of this strategy relies on the  $\eta^2$ -chelation of the alkene, bringing the allylic C–H bond close to the metal centre. In 2007, White reported the seminal example of intramolecular C–H allylic amination using the White (BisSO) $\bullet$ Pd(OAc)<sub>2</sub> catalyst **317**



(Scheme 70)<sup>348</sup>. A series of homoallylic *N*-tosyl carbamates **315** were cyclized to the corresponding vinyl oxazolidines **316** in good yields and diastereoselectivities (up to 86% yield, up to 18:1 *anti:syn*). Modulating the nucleophilicity of the nitrogen atom was pivotal to the success of the reaction. Mechanistic studies support (BisSO)•Pd(OAc)<sub>2</sub> mediated C–H bond cleavage to form the  $\pi$ -allyl-Pd species followed by counterion-mediated deprotonation of the tosylamide **318**. Subsequent *exo*-nucleophilic attack and reductive elimination furnished the product **316** and Pd<sup>0</sup>. Oxidation to the activate Pd<sup>II</sup>-catalyst was achieved using 1,4-benzoquinone **319** and acetic acid. The White group further expanded the scope to include 6-membered oxazinanone **320** products using *N*-nosyl substituents<sup>349</sup> as well as a tandem C–H amination/vinyllic arylation<sup>350</sup>. A rare complementary 7-membered ring forming C–H amination was reported by Liu in good yields and selectivities<sup>351</sup>. The use of NaOBz was found to be crucial in promoting the *endo*-cyclization.

## White (2007)

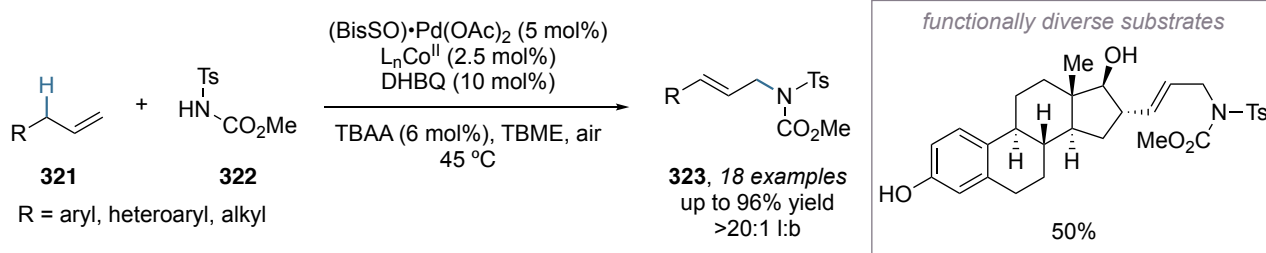


Scheme 70 | Pd-catalyzed intramolecular allylic C–H amination

Recent advancements by White have led to the development of a series of intermolecular C–H amination reactions. Remarkably, the same (BisSO)•Pd(OAc)<sub>2</sub> catalyst system was found to be effective for the intermolecular allylation of *N*-(methoxycarbonyl)tosylamides **322**, with linear alkenes **321**, in the presence of 1,4-benzoquinone **319**. Three generations of catalytic systems have been successively reported, the first employing a catalytic quantity of Cr<sup>III</sup>-salen as a Lewis acid<sup>352</sup>, and the second incorporating a tertiary amine base to increase the concentration of active nucleophile<sup>353</sup>. However, recent studies have revealed that in high concentrations benzoquinone can inhibit C–H amination, and so an innovative redox-relay protocol employing catalytic benzoquinone, Co<sup>II</sup> and O<sub>2</sub> as a terminal oxidant was implemented<sup>354</sup>. Under these conditions, linear allyl amines

**323** were selectively obtained in high yields (up to 96%) with good functional group tolerance, rendering it suitable for late-stage functionalization (Scheme 71).

White (2016)

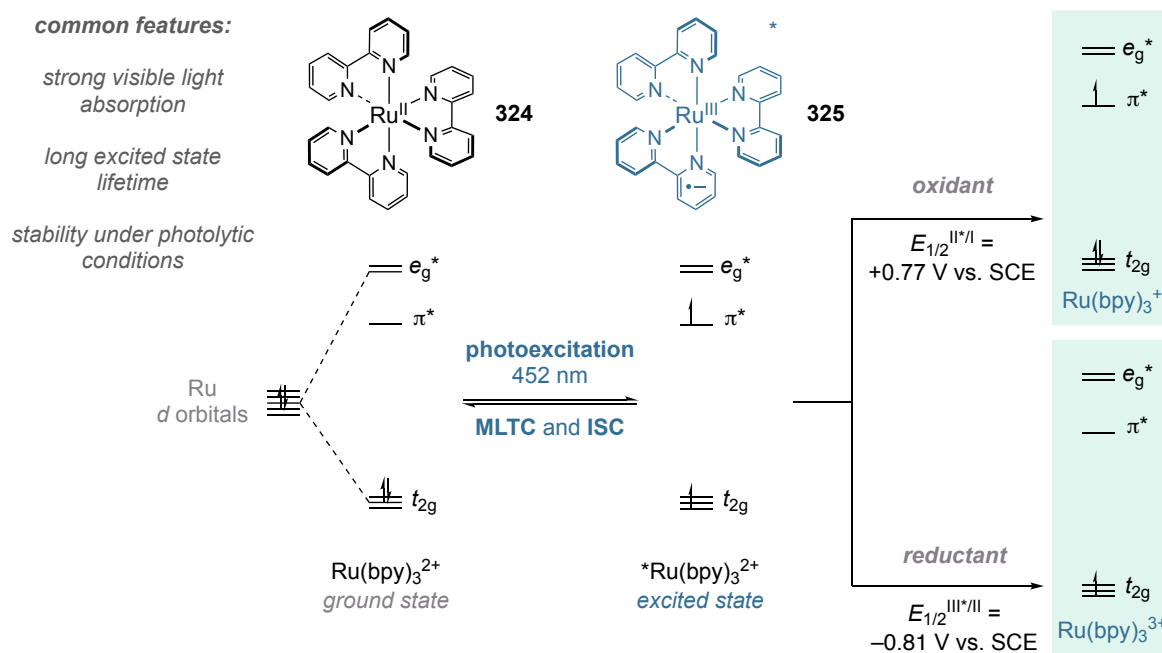


**Scheme 71** | Intermolecular Pd-catalyzed allylic C–H amination

#### 1.4 Transition-metal mediated visible light photoredox catalysis

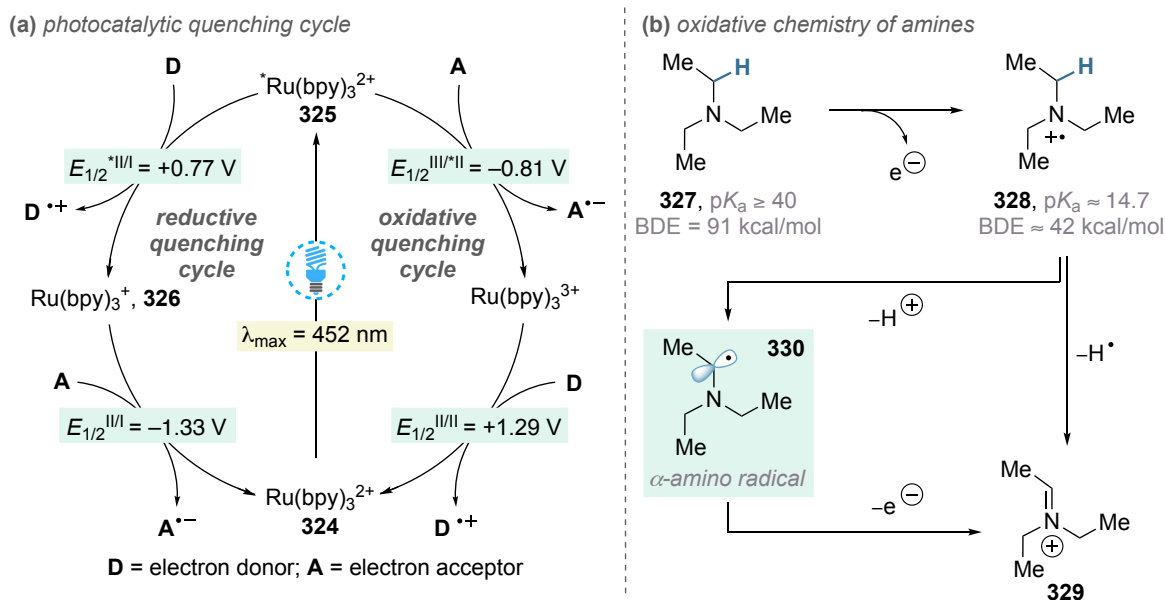
Over the last decade, visible light photoredox catalysis has garnered significant attention for the catalytic activation of organic molecules<sup>355</sup>. It should be noted that several elegant organic photoredox based catalytic systems for the construction of amines, most notably by Nicewicz<sup>356,357</sup>, have been reported and reviewed elsewhere<sup>358</sup>. The central paradigm of this approach relies on the ability of certain transition metal complexes to engage in a single electron transfer event (SET) with a suitable organic substrate upon photoexcitation. The majority of modern day photocatalysts are polypyridyl complexes of Ru(II)<sup>359</sup> and Ir(III)<sup>360</sup>, exemplified by Ru(bpy)<sub>3</sub><sup>2+</sup> **324**. These complexes, once excited by visible light, endure a sufficiently long-lived excited state **325** ( $\tau = 1100$  ns for Ru(bpy)<sub>3</sub><sup>2+</sup>) to engage in a productive bimolecular electron transfer<sup>361</sup>. In contrast to the ground state, the excited states of these molecules are both simultaneously potent single electron donors and acceptors; their relative strength modulated by the specific ligands coordinated to the metal centre (Scheme 72)<sup>362</sup>.

As evidenced by the redox cycle of Ru(bpy)<sub>3</sub><sup>2+</sup> **324**, the ground state reduction potential ( $E_{1/2}^{\text{III/I}} = -1.33$  V vs. SCE) is significantly more reducing than the excited state **325** ( $E_{1/2}^{\text{III/II}^*} = -0.81$  V vs. SCE) (Scheme 73a)<sup>363</sup>. Consequently, processes requiring strongly reducing conditions typically employ stoichiometric reductive quenchers to access the strongly reducing Ru<sup>I</sup>-species **326**. Historically, tertiary amines have served as sacrificial reductants as they are cheap, abundant and readily oxidized<sup>364</sup>. In recent years however, our understanding of the reactivity of amine radical cations has evolved to a level where we can now harness amines as substrates in new bond forming technologies<sup>365–367</sup>.



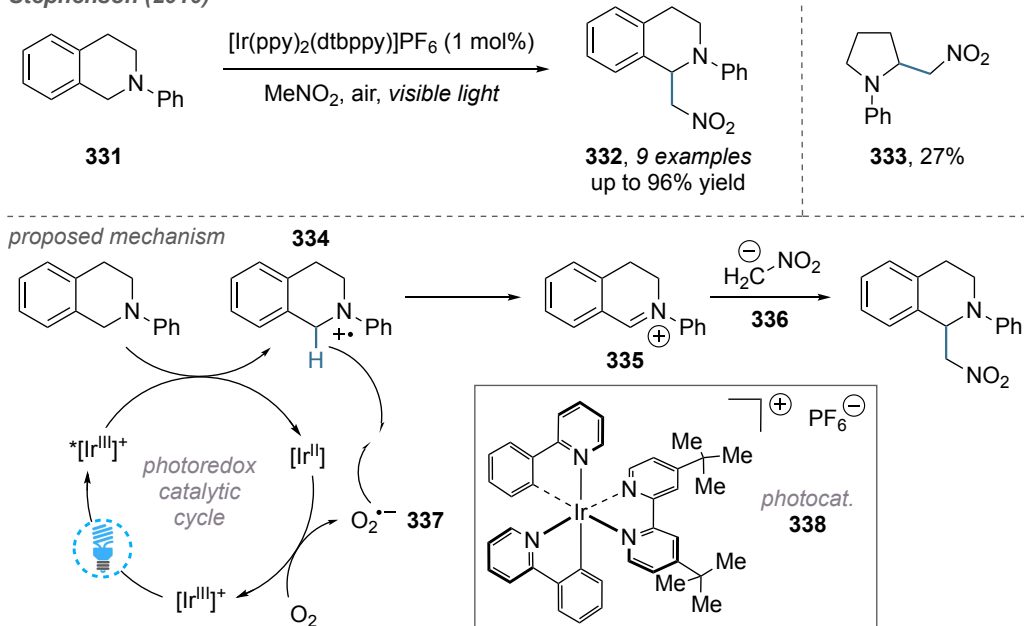
Scheme 72 | Overview of transition metal photocatalysts

Using triethylamine **327** as a simple example, oxidation to the radical cation **328** results in a dramatic acidification and weakening of the  $\alpha$ -amino C–H bonds [ $\text{p}K_{\text{a}} \approx 14.7$  (MeCN); BDE  $\approx 42$  kcal/mol]<sup>367</sup>. As such, this remarkable activation reveals a number of potential subsequent mechanistic pathways; H-atom abstraction to reveal an iminium ion **329** or deprotonation to reveal an  $\alpha$ -amino radical **330** (Scheme 73b)<sup>368</sup>.



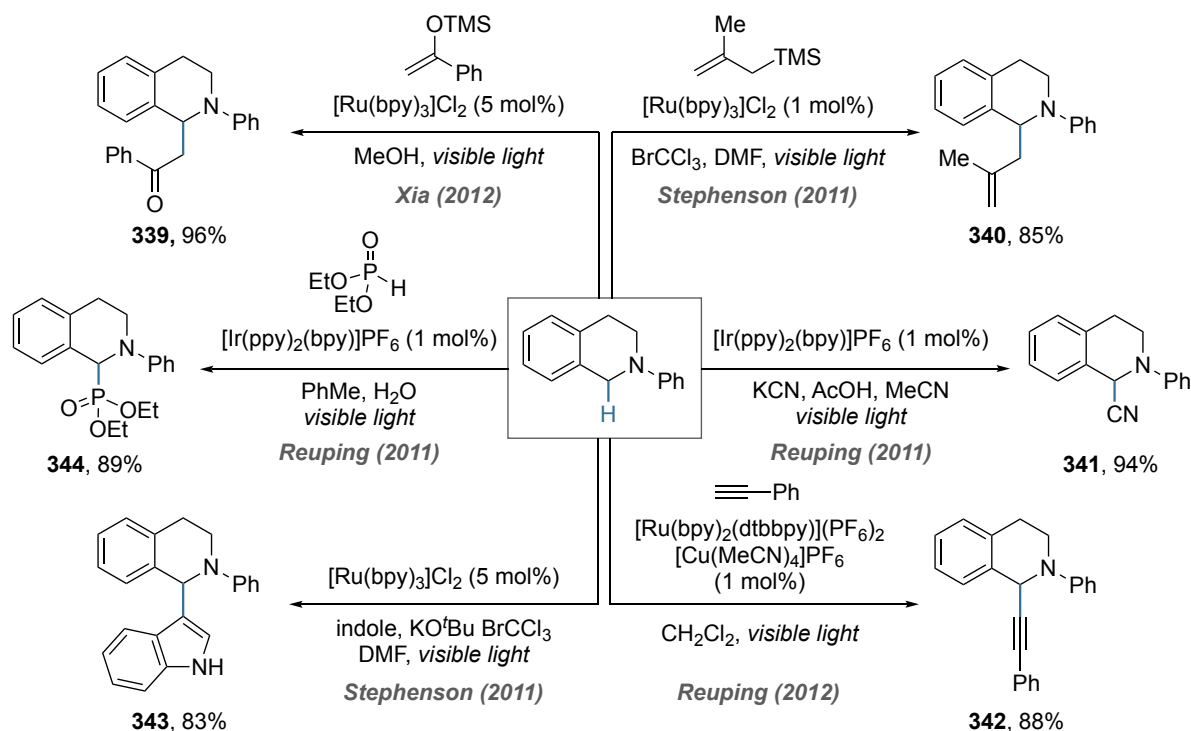
Scheme 73 | (a) Typical photocatalytic quenching cycle. (b) Oxidative chemistry of amines

## Stephenson (2010)



Scheme 74 | Photocatalytic Aza-Mannich reaction

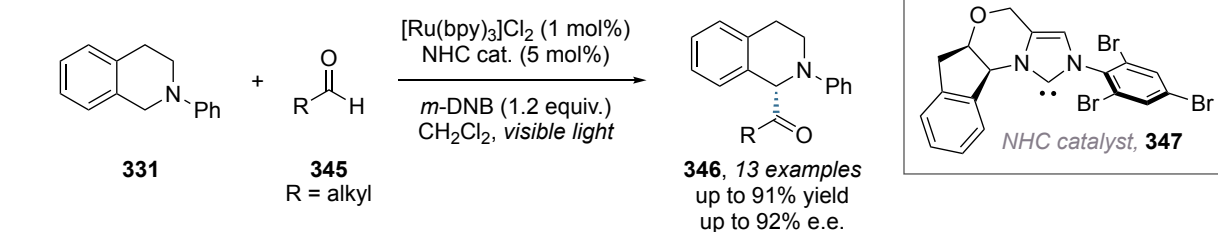
Among the most common photocatalytic transformations studied has been the addition of nucleophiles to catalytically generated iminium ions, directly installing a new C–C bond adjacent to the amine. The first report by Stephenson achieved an Aza-Henry reaction via the addition of nitromethane to *N*-aryltetrahydroisoquinolines **331** using an  $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$  photocatalyst **338** (Scheme 74)<sup>369</sup>. Mechanistically, oxidation of the tetrahydroisoquinoline generates the radical cation **334** and an  $\text{Ir}^{\text{II}}$  species that reduces  $\text{O}_2$  to its superoxide **337**, completing the photocatalytic cycle.



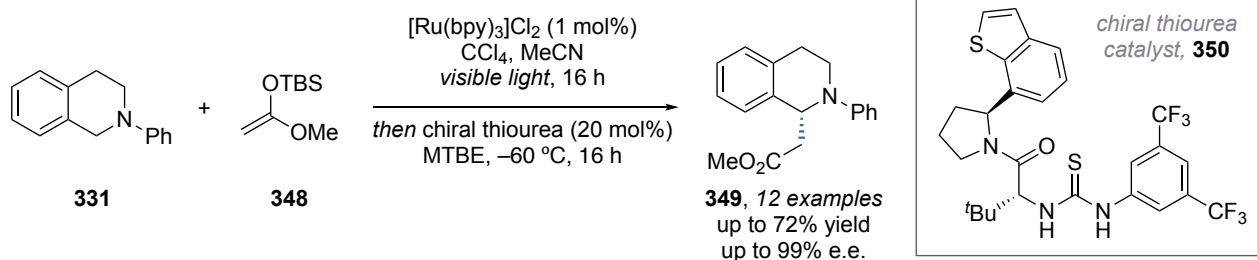
Scheme 75 | Overview of photocatalytic alkylamine functionalization

Subsequent hydrogen atom abstraction at the  $\alpha$ -position of the amine by  $\text{O}_2^{\bullet-}$  occurs exclusively to give the stable conjugated iminium ion **335**; addition of the nitromethane anion **336** delivers the aza-Henry product. The importance of the tetrahydroisoquinoline scaffold was highlighted by the substantially lower yields obtained when using *N*-phenylpyrrolidine (**333**). Accordingly, a series of related transformations using a plethora of nucleophiles has been reported, including the addition of cyanide (**341**)<sup>370</sup>, enol ethers (**339**)<sup>371</sup>, phosphites (**344**)<sup>372</sup>, alkynes (**342**)<sup>373</sup>, allyl silanes (**340**) and indoles (**343**) (Scheme 75)<sup>374</sup>.

(a) DiRocco & Rovis (2012)



(b) Jacobsen & Stephenson (2013)

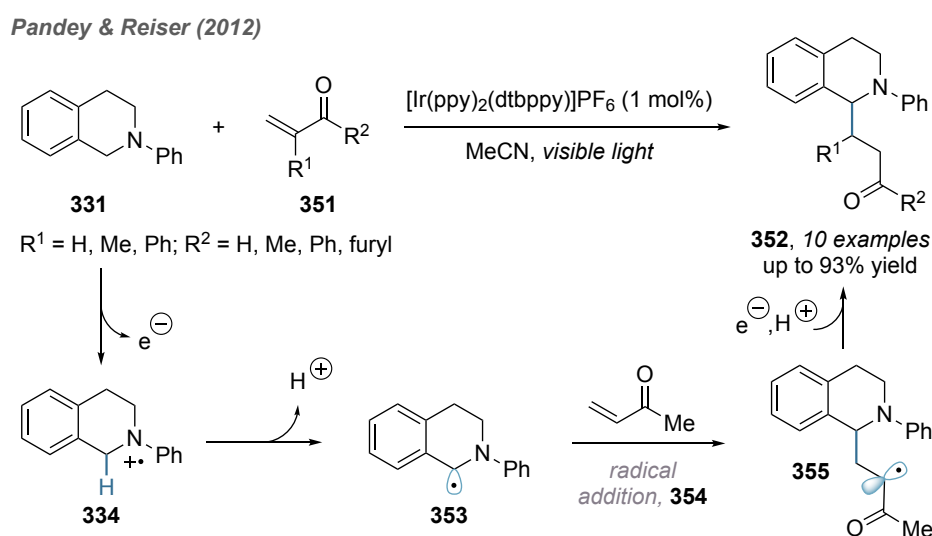


**Scheme 76** | (a) Photocatalytic chiral NHC-catalyzed  $\alpha$ -acylation. (b) Chiral anion binding amine functionalization

In 2012, DiRocco and Rovis devised an elegant strategy for the asymmetric  $\alpha$ -acylation of tertiary amines **331** via the merger of NHC and photoredox catalysis (Scheme 76a)<sup>375</sup>. Condensation of the NHC catalyst **347** with a range of simple aldehydes **345** generates the chiral acyl anion equivalent that reacts with the photocatalytically generated iminium ion (**346**) in good yields and high enantioselectivities (up to 91% yield, up to 92% e.e.). The authors found that addition of *m*-dinitrobenzene, as a weak organic oxidant, was crucial in inducing the oxidative quenching cycle of  $^*[\text{Ru}(\text{bpy})_3]^{2+}$ . An alternative strategy by Stephenson and Jacobsen in 2014 centred on the use of a chiral anion binding catalyst **350** to engage the iminium ion and generate a stereodefined chiral ion pair, subsequent attack by a silyl ketene acetal **348** gave the enantioenriched  $\beta$ -amino acid products **349** (up to 99% e.e.) (Scheme 76b)<sup>376</sup>.

Although  $\alpha$ -amino radicals frequently serve as an intermediary in the formation of iminium ions, they can also be employed as powerful reactive intermediates in their own right<sup>377</sup>. As a result of the donation of electron density from the nitrogen into the SOMO,  $\alpha$ -amino radicals are potent nucleophiles – representing an umpolung with respect to iminium ions. First reported independently

by Pandey and Reiser<sup>378</sup>, and Nishibayashi in 2012<sup>379</sup>, the reaction of *N*-aryl tertiary amines with  $\alpha,\beta$ -unsaturated carbonyl compounds, via catalytically generated  $\alpha$ -amino radicals, led to the corresponding addition products in good yields (Scheme 77). Similar to oxidative iminium ion formation, early results were obtained using *N*-aryltetrahydroisoquinolines **331**. A proposed mechanistic cycle involves oxidation of the tetrahydroisoquinoline to the radical cation **334** followed by deprotonation to the benzylic  $\alpha$ -amino radical **353**. Addition of the nucleophilic  $\alpha$ -amino radical to the electrophilic alkene **354** and subsequent exergonic reduction to the enolate anion **355** by Ir<sup>II</sup> furnishes the functionalized amine product **352** upon protonation.



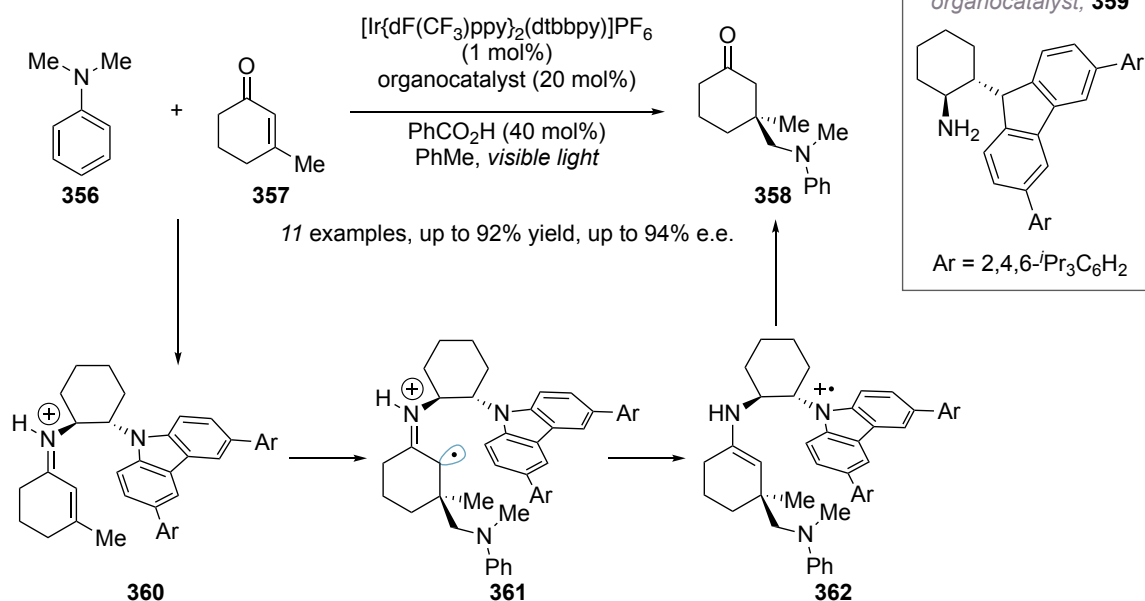
**Scheme 77** | Photocatalytic  $\alpha$ -amino radical generation and addition to electrophilic alkenes

Compared to iminium ions, the synthetic scope of  $\alpha$ -amino radical transformation is limited; the intermolecular addition of  $\alpha$ -amino radicals to simple  $\alpha,\beta$ -unsaturated carbonyl compounds is often low yielding, principally as a result of side reactions such as radical oligomerization<sup>380</sup>. Hence, strongly stabilizing radical acceptors such as alkylidene malonates and malononitriles are typically employed, as well as Brønsted acid activated systems<sup>381</sup>. Furthermore, the regioselectivity of  $\alpha$ -amino radical generation is dependent upon both kinetic and thermodynamic deprotonation, often leading to mixtures of products<sup>382</sup>. Therefore, heavily biased tetrahydroisoquinoline systems or symmetrical alkyl anilines are typically employed, reducing the overall synthetic utility of the transformation. Notwithstanding these challenges, several groups have reported similar  $\alpha$ -amine functionalization reactions utilizing allenolate<sup>383</sup>, vinyl pyridine<sup>384</sup> and maleimide<sup>385</sup> acceptors.

In 2016, Melchiorre reported an asymmetric addition of aniline-derived  $\alpha$ -amino radicals to cyclic enones using a combination of photoredox and chiral organocatalysis (Scheme 78)<sup>386</sup>. The activation of cyclic enones **357** was achieved using a dual-purpose chiral organocatalyst **359** bearing a bulky carbazole unit, forming an  $\alpha,\beta$ -unsaturated iminium ion **360**. At the same time, oxidation by the

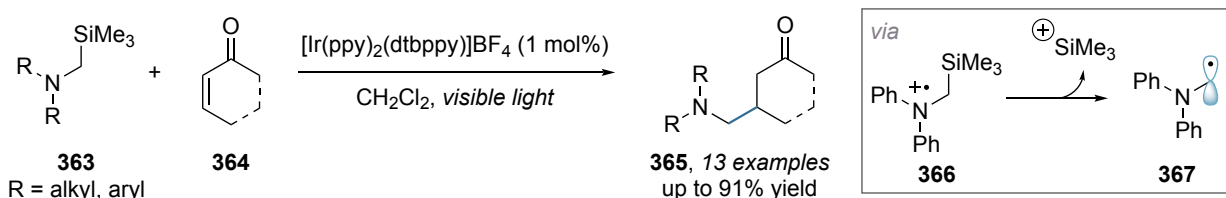
highly-oxidizing  $[\text{Ir}\{\text{dF}(\text{CF}_3)\text{ppy}\}_2(\text{dtbbpy})]\text{PF}_6$  photocatalyst and subsequent deprotonation of *N,N*-dimethylaniline **356** furnishes the  $\alpha$ -amino radical **361**, which adds enantioselectively to the iminium ion. Uniquely, the resulting iminyl radical **362** undergoes intramolecular electron transfer to the carbazole unit of the organocatalyst, the reduction of which closes the photocatalytic cycle. The corresponding products **358** were delivered in good yields and enantioselectivities (up to 92% yield, up to 94% e.e.).

Melchiorre (2016)

Scheme 78 | Photocatalytic asymmetric addition of  $\alpha$ -amino radicals to  $\alpha,\beta$ -unsaturated carbonyls

Due to the potential challenges associated with regioselective  $\alpha$ -amino radical generation, several groups have developed strategies using pre-installed electrofuges, the most common of which are  $\alpha$ -silyl amines **363**. In 2012, Nishibayashi reported that  $\alpha$ -amino radicals **367**, generated by the mesolytic desilylation of  $\alpha$ -silyl amine radical cations **366**, could add to  $\alpha,\beta$ -unsaturated carbonyl compounds **364** in good yields (Scheme 79)<sup>387</sup>. In this report, the products **365** were isolated as the corresponding silyl enol ethers. Moreover, the quantum yield was found to be high ( $\Phi = 0.68$ ), reflecting the efficient generation of  $\alpha$ -amino radicals using this photocatalytic platform.

Nishibayashi (2012)

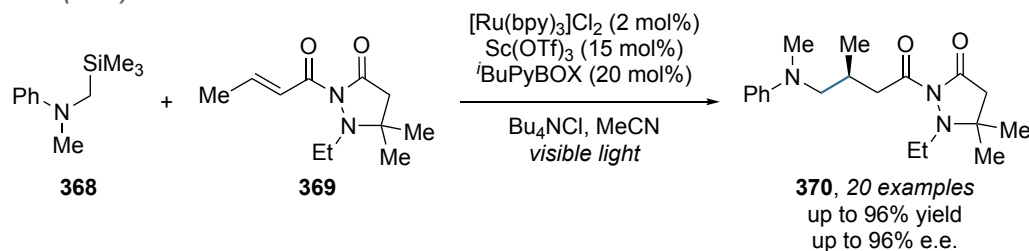
Scheme 79 | Photocatalytic  $\alpha$ -amino radical generation from  $\alpha$ -silyl amines

Additionally, in 2015 Yoon developed of an asymmetric version of the reaction, employing chiral Lewis acid and photoredox catalysis (Scheme 80)<sup>388</sup>. The reaction of  $\alpha$ -silyl amines **368** with  $\alpha,\beta$ -



unsaturated amides **369** using  $[\text{Ru}(\text{bpy})_3]\text{Cl}_2$  and a  $\text{Sc}^{\text{III}}$ -PyBOX catalyst yielded the radical addition products **370** in good yields and high enantioselectivities (up to 96% yield, up to 96% e.e.).

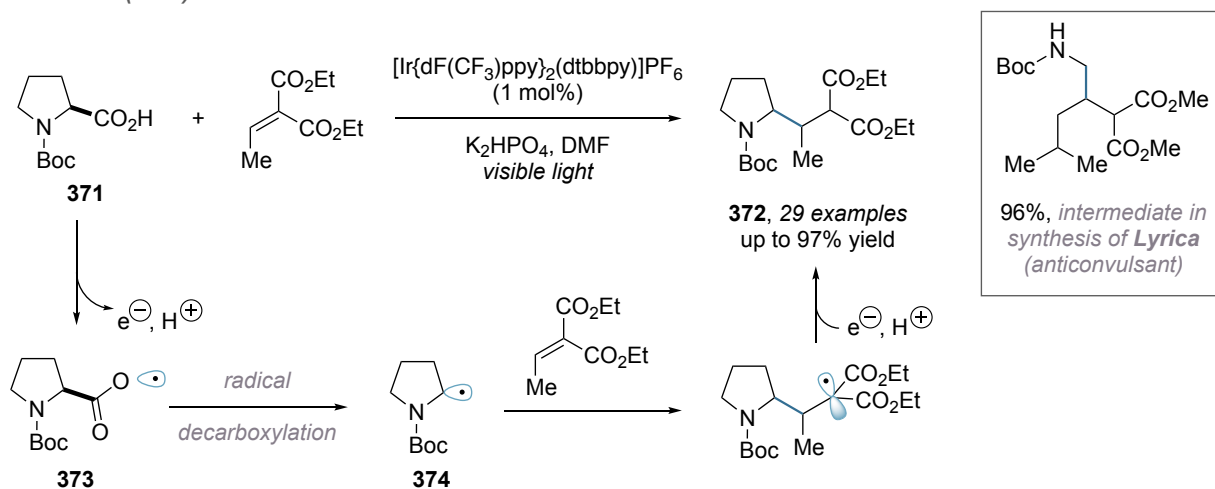
Yoon (2015)



**Scheme 80** | Asymmetric photocatalytic addition of  $\alpha$ -amino radicals to  $\alpha,\beta$ -unsaturated amides

A final strategy developed by MacMillan established the use of common  $\alpha$ -amino acids **371** as regioselective  $\alpha$ -amino radical precursors (Scheme 81)<sup>389</sup>. Unlike previous methodologies that rely upon oxidation of the amine, herein, oxidation of the carboxylate anion (**373**) followed by decarboxylative fragmentation generates the  $\alpha$ -amino radical **374** with high efficiency. Importantly, this method does not rely on the use of electron-rich aniline derivatives, greatly improving the scope of amine products **372** generated. A similar strategy using alkyl borates to generate  $\alpha$ -amino radicals in the presence of a photoredox catalyst was later reported by Akita<sup>390</sup>.

MacMillan (2014)



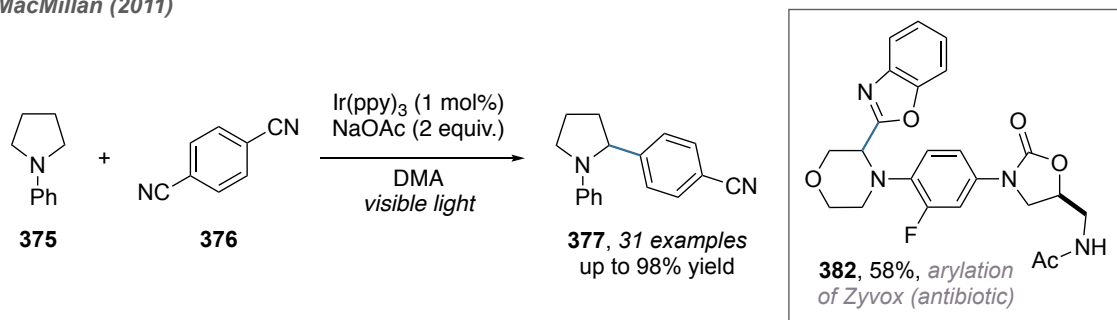
**Scheme 81** | Photocatalytic decarboxylative generation of  $\alpha$ -amino radicals

Importantly, the nucleophilicity of  $\alpha$ -amino radicals has led to the development of other methodologies employing a plethora of electrophiles beyond classical Michael acceptors. Whilst useful work has been accomplished by Nishibayashi<sup>391</sup>, Li<sup>392</sup>, Ooi<sup>393</sup>, and Meggers<sup>394</sup> on the addition of these radicals to azidodicarboxylates, isocyanates, and ketone/imine equivalents, some of the most versatile reactions have been achieved through photoredox-catalyzed aromatic substitution reactions.

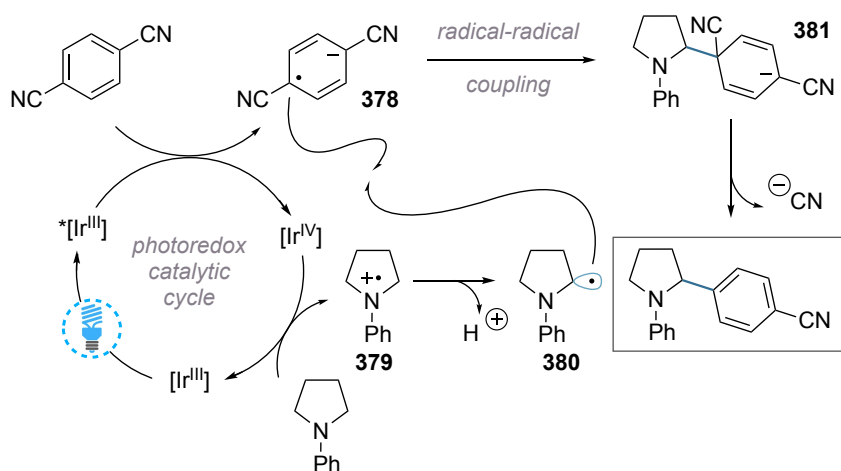


In 2011, MacMillan reported the photoredox catalyzed aromatic substitution of electron-deficient cyanoarenes **376** and heteroarenes with amines **375** via  $\alpha$ -amino radicals (Scheme 82)<sup>395</sup>. It was found that cyanoarenes effectively quenched the strongly reducing Ir(ppy)<sub>3</sub> photocatalyst, forming the arene radical anion **378**. Subsequent oxidation of the *N*-arylamine and deprotonation of the radical cation **379** generates the  $\alpha$ -amino radical **380**; radical-radical cross coupling **381** and elimination of the cyanide anion yields the  $\alpha$ -arylated amine product **377**. The scope of the reaction is varied, with good yields obtained for more electron-poor morpholine and piperazine scaffolds **382** as well as impressive regioselectivities using ‘all-alkyl’ tertiary amines. The scope was further extended to incorporate heteroaryl halides<sup>396</sup>, as well as  $\alpha$ -amino acids<sup>397</sup>, as coupling partners.

MacMillan (2011)



proposed mechanism

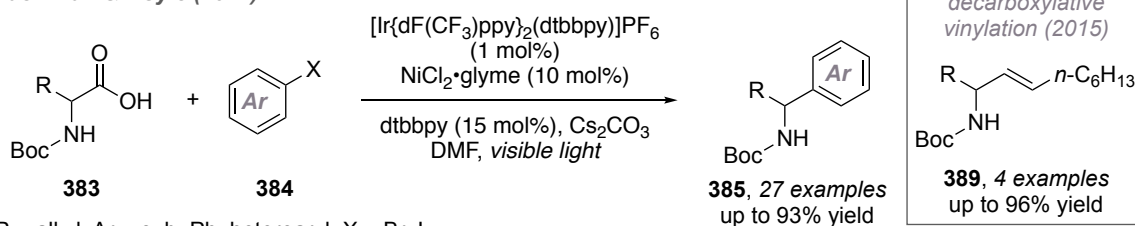


**Scheme 82** | Dual photocatalytic/transition metal catalyzed  $\alpha$ -arylation of amines

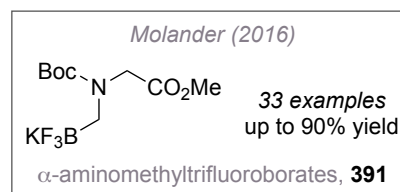
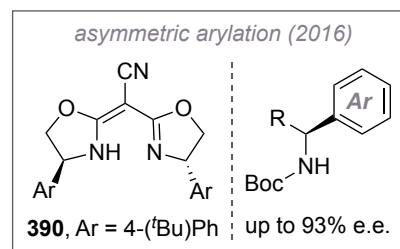
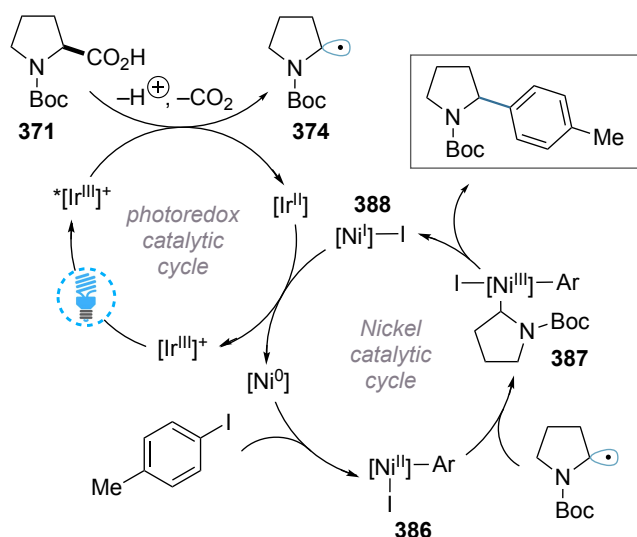
In 2014, MacMillan and Doyle published seminal work on the merger of photoredox and transition metal catalysis (Scheme 83)<sup>398</sup>. Using nickel, due to its ability to undergo both single and two-electron oxidations/reductions,  $\alpha$ -amino acids **383** were successfully arylated using simple aryl and heteroaryl halides **384** in good yields. Fu and MacMillan later described the use of a chiral bis-oxazoline ligand **390** at nickel to render the transformation enantioselective<sup>399</sup>. Mechanistically, oxidative decarboxylation of the  $\alpha$ -amino acid was achieved using a highly oxidizing [Ir{dF(CF<sub>3</sub>)ppy}<sub>2</sub>(dtbbpy)]PF<sub>6</sub> photocatalyst, generating the  $\alpha$ -amino radical **374**. At the same time, oxidative addition of the aryl halide to Ni<sup>0</sup> generates an electrophilic Ni<sup>II</sup>-aryl species **386** that reacts

with the  $\alpha$ -amino radical to form a  $\text{Ni}^{\text{III}}$ -complex **387**. Reductive elimination of the product yields a  $\text{Ni}^{\text{I}}$ -halide intermediate **388** that is reduced by the  $\text{Ir}^{\text{II}}$ -photocatalyst to the active  $\text{Ni}^0$  species and simultaneously closing the photocatalytic cycle. Vinyl halides were also shown to be competent substrates (**389**) under modified reaction conditions. Molander further devised a similar protocol employing dual photoredox and Ni-catalysis using  $\alpha$ -aminomethyltrifluoroborates **391** as  $\alpha$ -amino radical precursors<sup>400</sup>.

MacMillan & Doyle (2014)



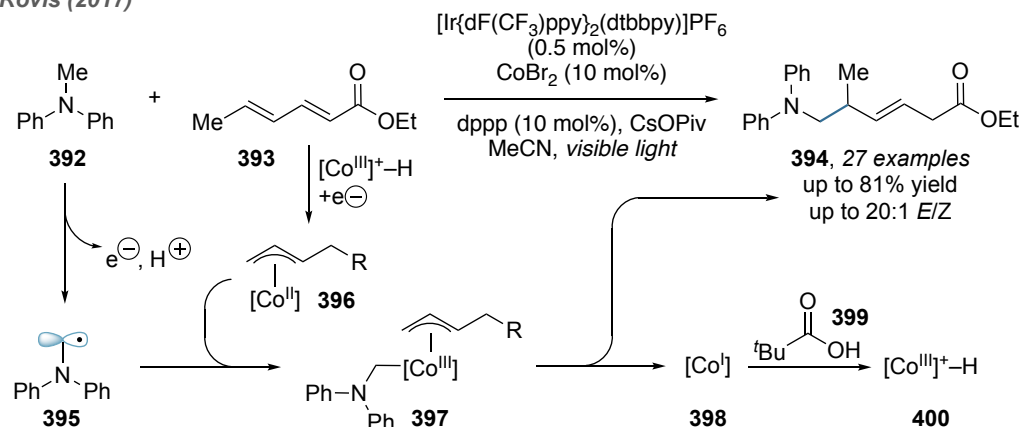
proposed dual photoredox/nickel catalytic cycle



**Scheme 83** | Photocatalytic decarboxylative arylation of  $\alpha$ -amino acids

Recently, Rovis demonstrated that combined photoredox/transition metal catalysis could be harnessed for the hydroaminoalkylation of 1,3-dienes **393** with tertiary amines **392** (Scheme 84)<sup>401</sup>.

Rovis (2017)

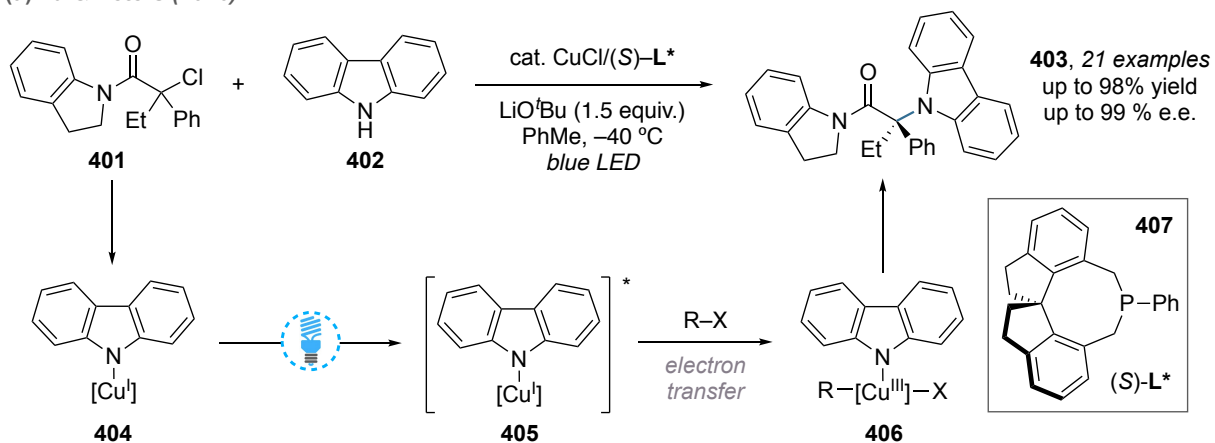


Scheme 84 | Dual photocatalytic/Co-catalyzed aminomethylation of 1,3-dienes

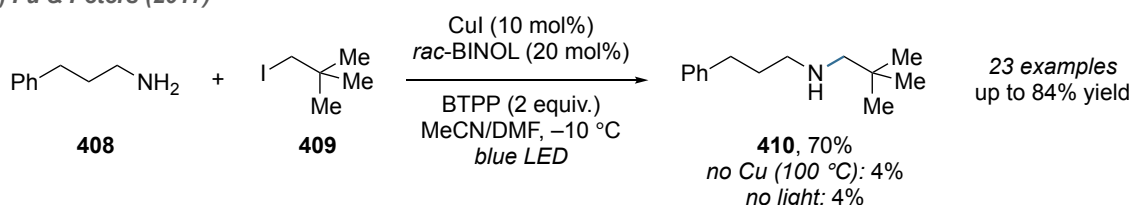
Given cobalt's predilection for 1,3-dienes, as well as its range of accessible oxidation states, its union with oxidative amine photoredox catalysis gave rise to a series of complex amine products **394**. A proposed mechanism involved oxidative addition of pivalic acid **399** to  $\text{Co}^{\text{I}}$ , generating a cationic  $\text{Co}^{\text{III}}\text{-H}$  species **400** that adds to a 1,3-diene furnishing a  $\pi$ -allyl- $\text{Co}^{\text{II}}$  complex **396** upon photocatalytic reduction. Subsequent reaction with the  $\alpha$ -amino radical **395** affords a  $\text{Co}^{\text{III}}$  complex **397**, which upon reductive amination, delivers the product and active  $\text{Co}^{\text{I}}$  catalyst **398**.

While the union between transition metal and photoredox catalysis has enabled the construction of unique C–C bonds, pioneering work by Fu and Peters in 2012 revealed that catalytic  $\text{C}(\text{sp}^2)\text{-N}$  bond formation could be accomplished using a combination of Cu and visible light, without the need for an external photocatalyst<sup>402</sup>. Subsequent optimization led to the development of competent conditions for the photoinduced Cu-catalyzed alkylation of a variety of alkyl halides using carbazoles<sup>403</sup> and amides<sup>404</sup>. In 2016, Fu and Peters disclosed the asymmetric Cu-catalyzed cross-coupling of tertiary alkyl halides **401** with amines **402**, generating amines bearing fully-substituted stereocenters **403** in high yields and enantioselectivities (up to 98% yield, up to 99% e.e.) (Scheme 85a)<sup>405</sup>. Using a Cu/chiral phosphine catalyst **407**, visible-light excitation of the  $[\text{Cu}^{\text{I}}]\text{-carbazole}$  complex **404** to its excited state **405** leads to SET with the alkyl halide. The authors postulate that coupling between the nucleophile and alkyl radical can be achieved via an inner-sphere radical pathway, possibly involving a Cu-nucleophile complex **406**. However, recent evidence suggests that an out-of-cage  $\text{Cu}^{\text{II}}$ -catalyzed coupling between the alkyl and carbazyl radicals may be operative<sup>406</sup>. In 2017, the scope of the transformation was extended to include the coupling of simple primary alkylamines **408** with alkyl halides **409**, forming the corresponding secondary amines **410** in good yields where classical alkylation failed to deliver the desired products (Scheme 85b)<sup>407</sup>.

## (a) Fu &amp; Peters (2016)

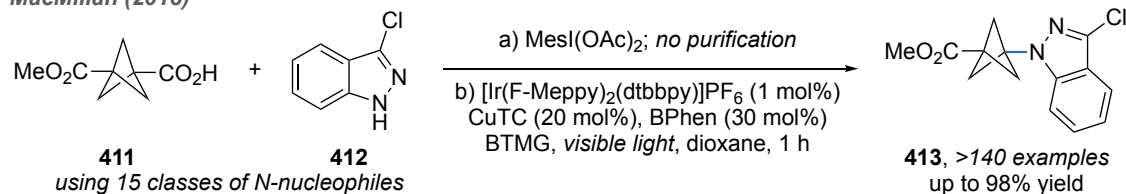
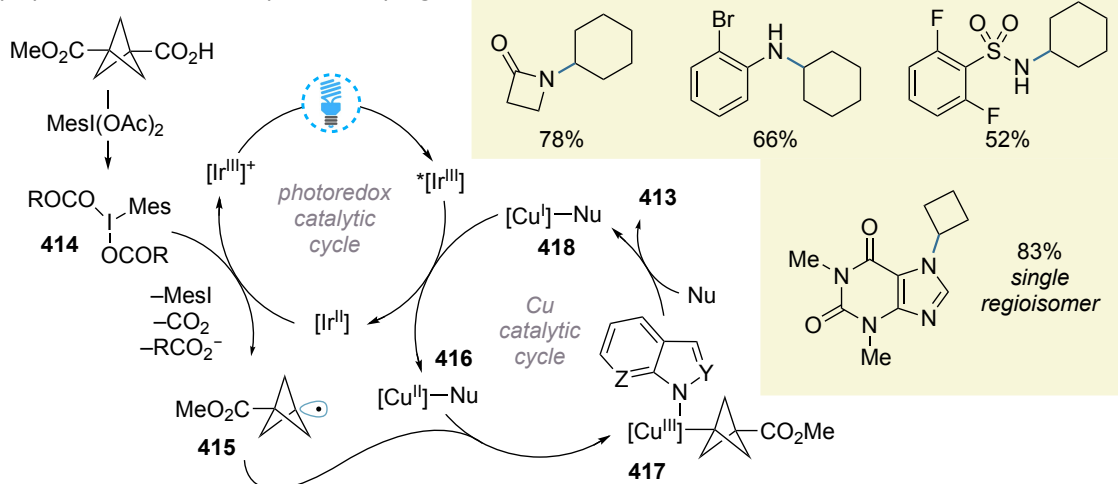


## (b) Fu &amp; Peters (2017)

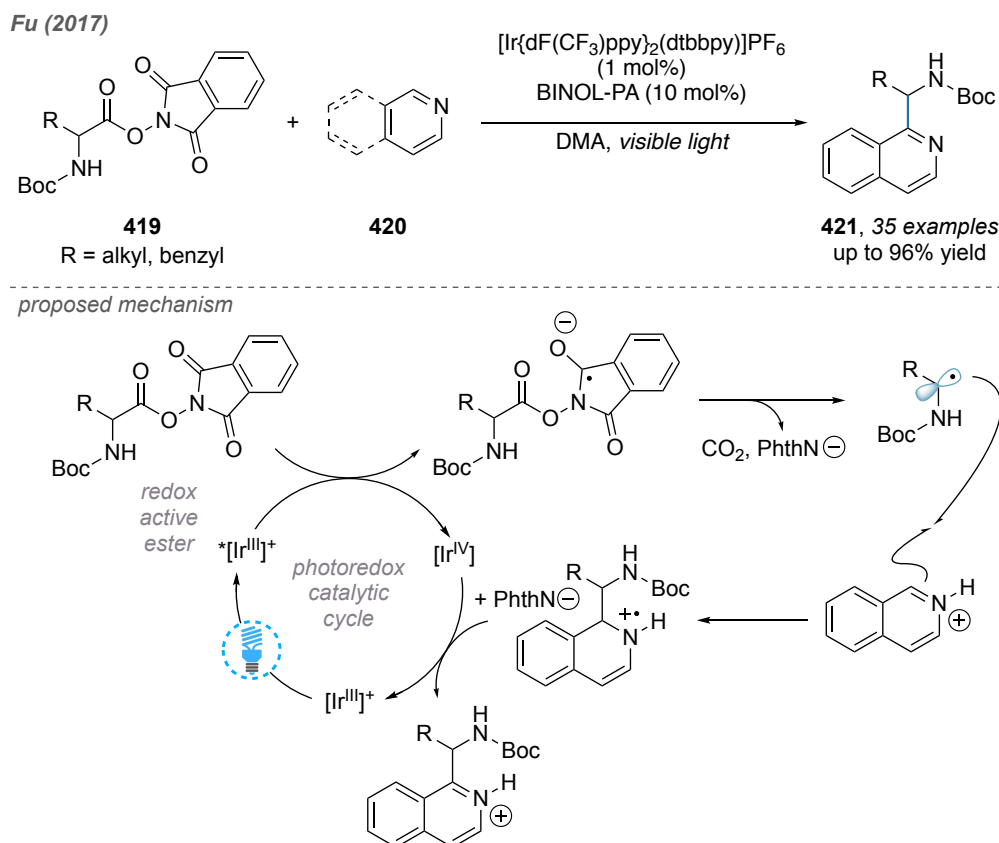
**Scheme 85** | (a) Asymmetric Cu-catalyzed cross-coupling of alkyl halides. (b) Photoinduced alkylation of alkylamines

In 2018, Hu<sup>408</sup> and MacMillan<sup>409</sup> independently reported the dual Cu/photoredox catalyzed C(sp<sup>3</sup>)-N cross-coupling of amines **412** and carboxylic acids **411** (Scheme 86). Although different decarboxylation strategies were employed to access the desired alkyl radical, the use of pre-formed iodomesitylene dicarboxylates **414** by MacMillan enabled facile coupling with a wide variety of nitrogen-based nucleophiles under mild conditions (>140 examples, up to 98% yield). The authors propose that upon photocatalytic oxidation of the Cu<sup>I</sup>-amine species **418** to Cu<sup>II</sup>, SET to the iodomesitylene dicarboxylate, followed by the extrusion of CO<sub>2</sub>, MeI, and carboxylate, generates the desired alkyl radical **415**. Capture of the alkyl radical by the Cu<sup>II</sup>-amine species **416**, generating a Cu<sup>III</sup>-complex **417**, furnishes the desired product **413** upon reductive elimination. Interestingly, several of the corresponding amine products could not be accessed via classical S<sub>N</sub>2 and S<sub>N</sub>1 alkylation conditions, highlighting the potential utility of this complementary approach.

MacMillan (2018)

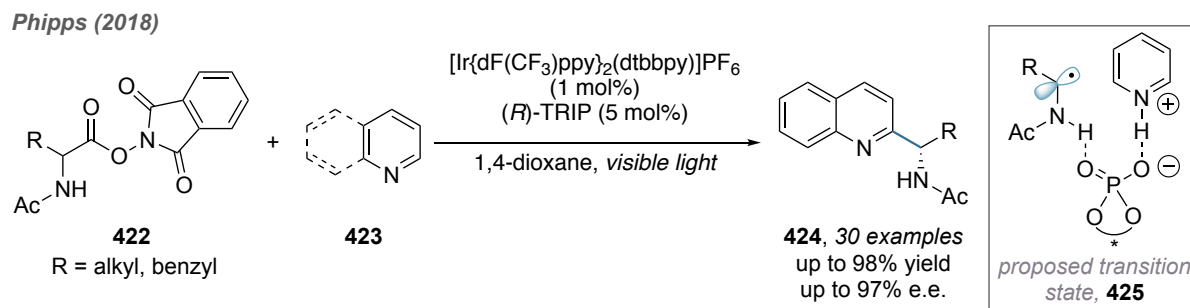
proposed mechanism for *sp*<sup>3</sup> C–N coupling**Scheme 86** | Dual Cu/photoredox catalyzed cross-coupling of amines and carboxylic acids

The regioselective alkylation of *N*-heteroarenes is of paramount importance to the medicinal chemistry community<sup>410</sup>. In this context, the Minisci reaction – where an oxidatively generated alkyl radical attacks a protonated heteroarene to afford the alkylated product upon oxidation, is a well-established process<sup>411</sup>. However, the analogous reaction with  $\alpha$ -amino radicals has been hampered by the use of strong stoichiometric oxidants and sluggish reactivity<sup>412</sup>. Given the mild and manageable reactivity associated with photoredox catalysis, several procedures have been developed for the  $\alpha$ -aminoalkylation of *N*-heteroarenes. As the final step of the Minisci reaction involves oxidative aromatization, the  $\alpha$ -amino must be accessed via a reductive pathway; the most common of which are  $\alpha$ -amino acid-derived *N*-hydroxyphthalimide esters, so-called “redox-active esters” **419**<sup>413</sup>.



Scheme 87 | Photocatalytic Minisci-type addition of redox active esters

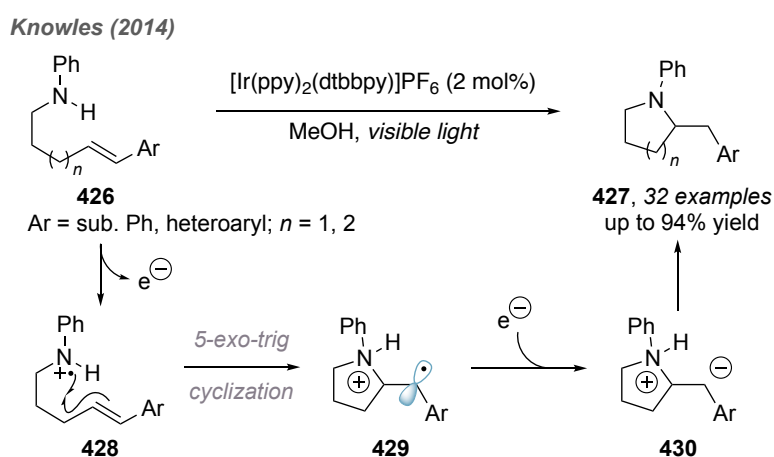
In 2017, Fu reported the dual Photoredox/Brønsted acid co-catalyzed decarboxylative coupling of activated  $\alpha$ -amino acids **419** with *N*-heteroarenes **420** in good yields and excellent functional group compatability (up to 96% yield) (Scheme 87)<sup>414</sup>. Using a  $[\text{Ir}\{\text{dF}(\text{CF}_3)\text{ppy}\}_2(\text{dtbbpy})]\text{PF}_6$  photocatalyst and a bulky BINOL-derived phosphoric acid co-catalyst, the efficacy of which is ascribed to facile proton-shuttling from the more sterically encumbered product to the substrate, a variety of di- and tripeptides, as well as drug molecules, were functionalized successfully (**421**).

Scheme 88 | Asymmetric photocatalytic addition of  $\alpha$ -amino radicals to heteroarenes

In 2018, Phipps described the asymmetric  $\alpha$ -aminoalkylation of *N*-heteroarenes **423** with activated  $\alpha$ -amino acids **422** using a dual photoredox/chiral phosphoric acid catalyst (Scheme 88)<sup>415</sup>. Pivotal to the success of the transformation was a key hydrogen-bonding interaction between the chiral acid, acidic *N*-acetyl protected  $\alpha$ -amino radical and pyridine substrate **425**. The corresponding alkylated

products **424** were obtained in excellent yields and enantioselectivities (up to 98% yield, up to 97% e.e.).

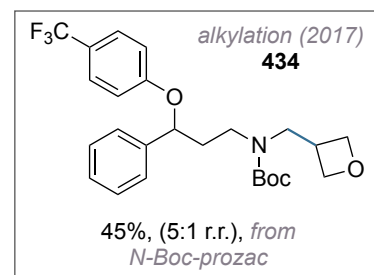
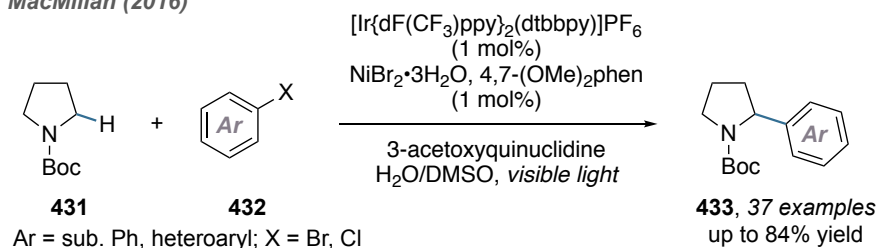
In 2014, Knowles reported an alternative bond-forming tactic derived from amine radical cations (Scheme 89). Using a  $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$  photocatalyst, oxidation of a secondary alkyl aniline **426** resulted in the formation of an electrophilic amine radical cation **428** that underwent intramolecular *anti*-Markovnikov hydroamination of vinyl arenes, generating a benzylic radical **429**<sup>416</sup>. Subsequent single electron reduction to the zwitterionic pyrrolidine **430** furnishes the product **427** upon proton transfer. The reaction proved general for both 5- and 6-*exo*-trig cyclizations as well as heteroatom substituted ring systems.



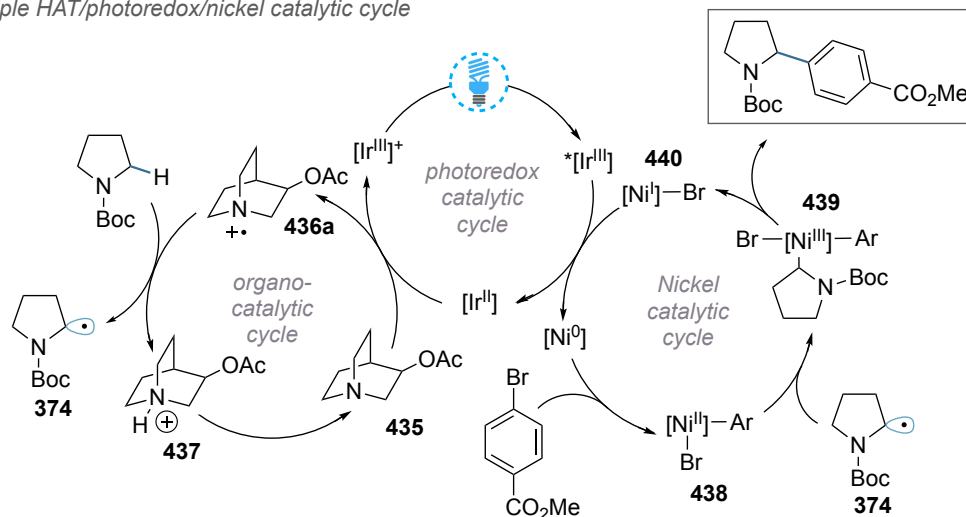
Scheme 89 | Photocatalytic intramolecular hydroamination of vinyl arenes

In 2016, MacMillan detailed the triple catalytic cross coupling of Boc-protected amines **431** and aryl halides **432** (Scheme 90)<sup>417</sup>. In combination with transition metal and photoredox catalysis, generation of the key  $\alpha$ -amino radical was achieved via HAT catalysis. Photocatalytic oxidation of 3-acetoxyquinuclidine **435** generates a sufficiently electron-deficient radical cation **436a** that it is able to engage nucleophilic  $\alpha$ -amide C–H bonds in a kinetic HAT, delivering the  $\alpha$ -amino radical **374** and quinuclidinium cation **437**. Addition of the radical to an  $(\text{aryl})\text{Ni}^{\text{II}}\text{--Br}$  intermediate **438** furnishes the product upon reductive elimination from  $\text{Ni}^{\text{III}}$ -species **439** and photocatalytic reduction of the  $\text{Ni}^{\text{I}}$ -complex **440** closes the photocatalytic cycle. The system showed impressive selectivity across a range of substrates, including a kinetic preference for methyl HAT over methylene, as well as methylene HAT over methine. The same strategy was later extended to the use of alkyl halides as coupling partners (**434**)<sup>418</sup>.

MacMillan (2016)



proposed triple HAT/photoredox/nickel catalytic cycle

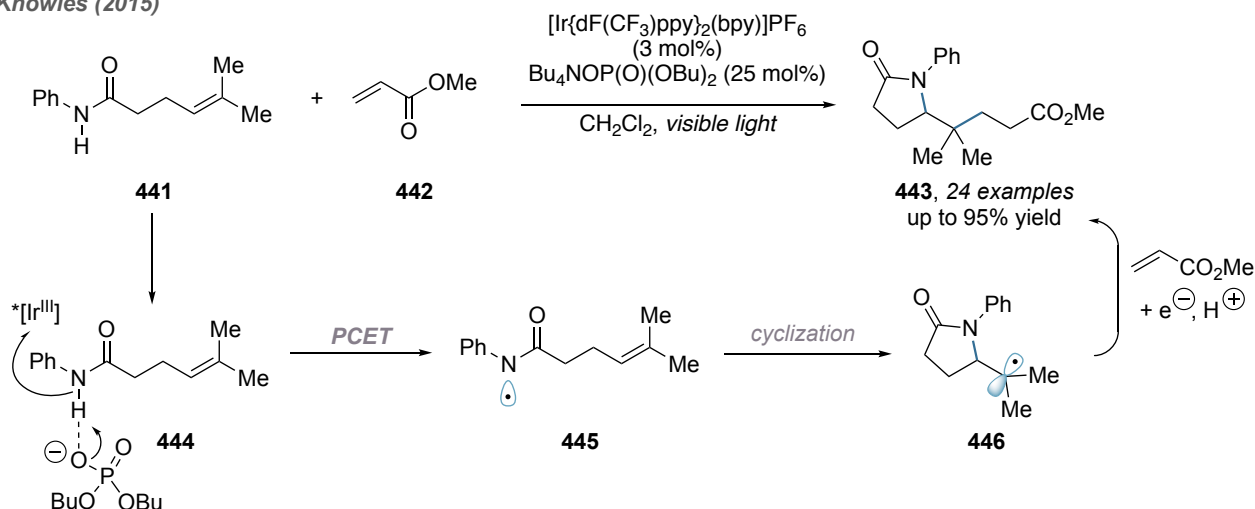


Scheme 90 | Triple HAT/photoredox/Ni-catalyzed arylation of Boc-protected amines

While HAT remains a powerful method for homolytic bond cleavage, its primary limitation is selectivity, abstracting weaker C–H bonds preferentially<sup>419</sup>. An alternative strategy based on proton-coupled electron transfer (PCET) operates via an alternative mechanism that addresses this limitation directly<sup>420</sup>. In PCET oxidations, an electron and proton originating from a single species are transferred to two separate acceptors – a Brønsted base and a single-electron oxidant, in one concerted step. Manifestly, the loss of H· is common between the two processes, however the chemoselectivity is distinct, as PCET requires the formation of a hydrogen bond between the substrate proton and base prior to electron transfer. Therefore, strong X–H bonds (X = O, N; BDFE ~ 100 kcal/mol) that are impervious to HAT are now rendered susceptible to PCET<sup>421</sup>. In 2015, Knowles reported the photocatalytic carboamination of alkenes **441** enabled via PCET (Scheme 91)<sup>422</sup>. Employing a combination of  $[\text{Ir}\{\text{dF}(\text{CF}_3)\text{ppy}\}_2(\text{bpy})]\text{PF}_6$  photocatalyst and a soluble dibutylphosphate base, PCET homolysis of an amide N–H bond **444** could be achieved, liberating the amidyl radical **445**. Cyclization onto the pendant alkene (**446**) and intermolecular radical addition to an  $\alpha,\beta$ -unsaturated carbonyl compound **442** generates the corresponding  $\alpha$ -ester radical; reduction by the Ir<sup>II</sup>-photocatalyst and protonation generates the desired product **443**.



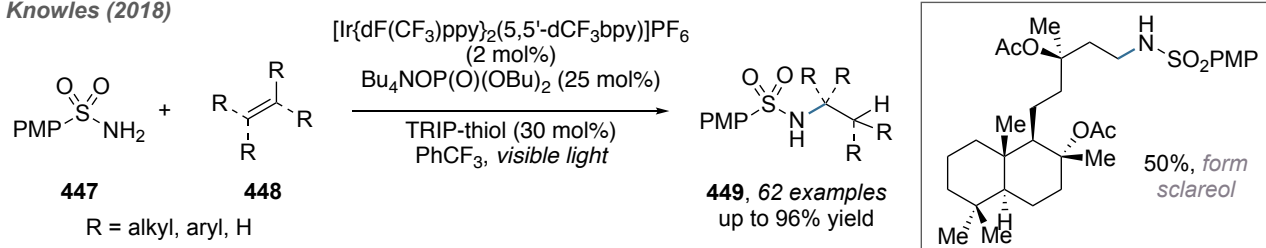
Knowles (2015)



Scheme 91 | Photocatalytic PCET mediated carboamination of alkenes

The same year, Knowles detailed the photocatalytic intramolecular hydroamidation of similar alkenyl amides via a PCET strategy using a thiol based H-atom donor<sup>423</sup>. Recently, Knowles described the intermolecular *anti*-Markovnikov hydroamination of unactivated alkenes 448 with more reactive sulphonamides 447 (Scheme 92)<sup>424</sup>. Using a bespoke ( $[\text{Ir}\{\text{dF}(\text{CF}_3)\text{ppy}\}_2(5,5'\text{-dCF}_3\text{bpy})]\text{PF}_6$ ) photocatalyst, dibutyl phosphate base and hindered TRIP-thiol H-atom donor 453, an array of simple and complex aliphatic alkenes underwent hydroamination in moderate to good yields (449) (up to 96%).

Knowles (2018)

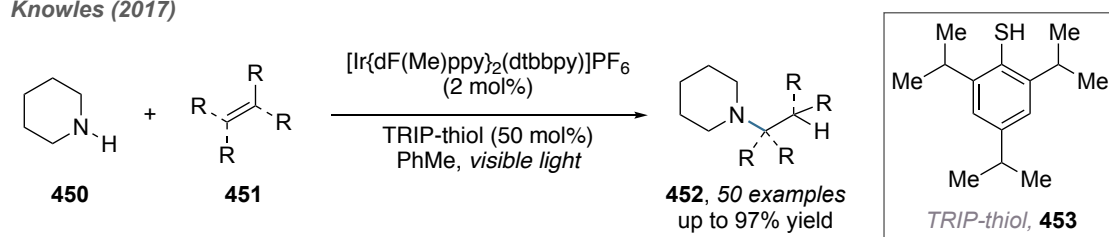


Scheme 92 | Photocatalytic intermolecular hydroamidation

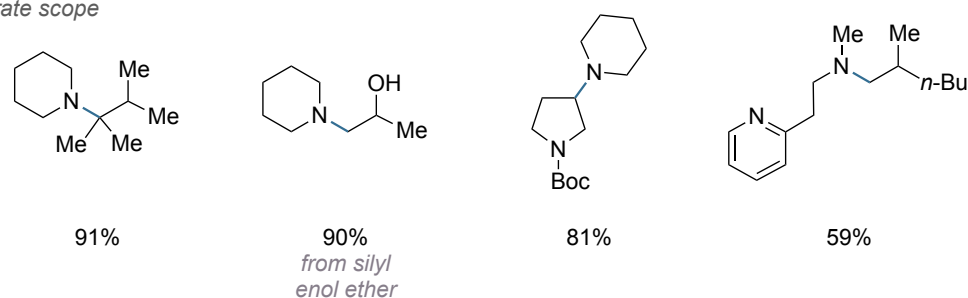
In 2017, Knowles revealed a catalytic intermolecular *anti*-Markovnikov hydroamination of unactivated alkenes 451 with secondary alkylamines 450 – a remarkably challenging transformation due to unfavourable thermodynamics (Scheme 93)<sup>425</sup>. Contrary to aniline-derived aminium radical cations, the equivalent species derived from the oxidation of dialkylamines yielded aminium radical cations that were found to undergo addition to a variety of alkene acceptors on a competitive timescale to unproductive back electron transfer. Moreover, the characteristic electrophilic character of aminium radical cations leads to high levels of *anti*-Markovnikov selectivity. Unlike the intramolecular cyclization onto vinyl arenes, the use of unactivated alkenes requires a H-atom donor; however, this presents a hypothetical challenge due to competitive HAT from the aminium radical

cation. Fortuitously, hindered TRIP-thiol catalyst **453** was found to function effectively as a H-bond donor, likely as a result of mismatched polar effects. The scope was found to be particularly broad, facilitating the hydroamination of hindered tetrasubstituted alkenes, silyl enol ethers and vinyl amides (**452**) in good yields.

Knowles (2017)



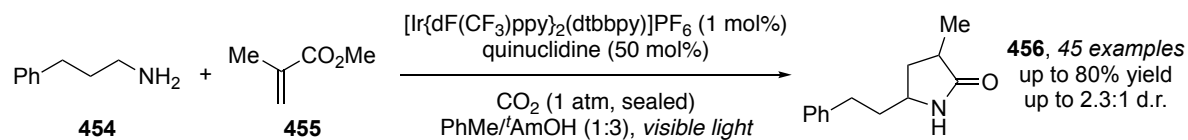
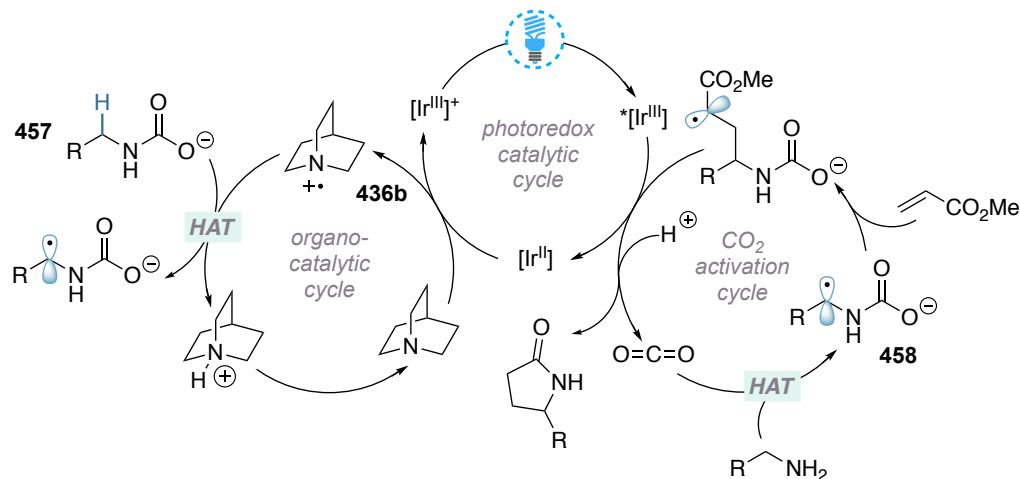
substrate scope



**Scheme 93** | Photocatalytic intermolecular hydroamination of alkylamines

Recently, Rovis developed a direct photocatalytic annulation strategy for the synthesis of  $\gamma$ -lactams **456** from primary amines **454** and acrylates **455** in good yields and moderate diastereoselectivities (up to 80% yield, up to 2.3:1 d.r.) (Scheme 94)<sup>426</sup>. Utilizing  $\text{CO}_2$ , the *in-situ* formation of a carbamate **457** was found to accelerate C–H bond activation via HAT through an electrostatic interaction with the quinuclidinium radical cation **436b**. Subsequent addition of the  $\alpha$ -amino radical **458** to the acrylate, followed by SET, leads to the corresponding  $\gamma$ -lactam upon decarboxylation/cyclization.

Rovis (2018)

proposed triple HAT/photoredox/ $\text{CO}_2$  activation catalytic cycle

Scheme 94 | Photocatalytic annulation of primary amines and acrylates

### 1.5 Conclusion and outlook

Over the last 50 years, transition metal catalysis has evolved from an academic curiosity to the vanguard of modern organic synthesis. The unique reactivity of these elements towards  $\pi$ -systems, unreactive  $sp^2$ -halides, bulk gases ( $\text{CO}$ ,  $\text{H}_2$ ), inert C–H bonds and visible light, combined with the ability to create a chiral environment, continues to enable previously inconceivable molecular disconnections – facilitating the rapid and cost-effective synthesis of natural products, pharmaceuticals and functional materials<sup>427</sup>. To this end, transition metal catalysts have greatly enhanced the capacity for complex amine synthesis from readily available feedstocks, although significant synthetic challenges still remain.

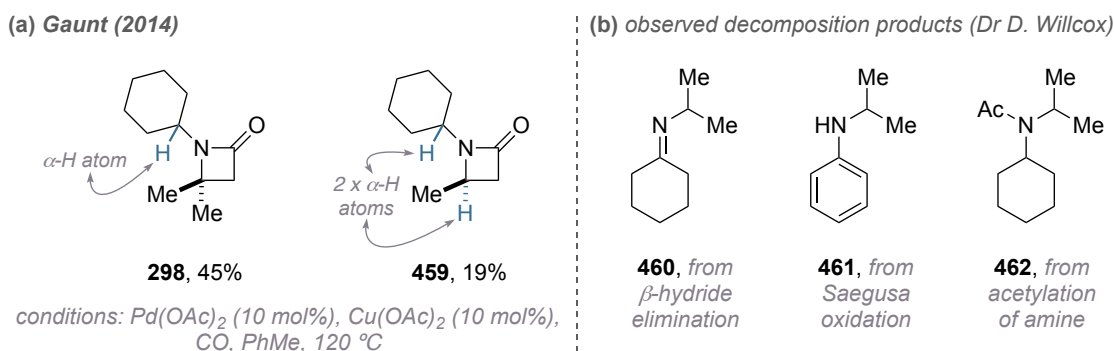
Namely, the development of hydroamination protocols employing ammonia presents a formidable challenge due to its low nucleophilicity compared to the alkylamine products. Moreover, further efforts are required for the development of more general *anti*-Markovnikov and intermolecular asymmetric processes. In addition, the development of effective hydroaminomethylation technologies, including asymmetric transformations, that can be implemented under mild conditions are highly sought after. While emerging C–H activation methodologies have grown exponentially over the last decade, the direct C–H amination of complex molecules in the presence of labile functional groups would undoubtedly revolutionize the field. Furthermore, the site-selective C–H

activation of more challenging  $\beta$ -positions as well as remote positions, especially asymmetrically, would be of great value for last-stage functionalization. Besides direct metal-mediated C–H functionalization, the expansion of amine based visible light photocatalysis, including increased selectivity in more complex systems as well as the development of enantioselective transformations, would have far-reaching implications across the synthetic community.

## 2 Pd<sup>II</sup>-catalyzed carbonylation of methylene β-C–H bonds in alkylamines

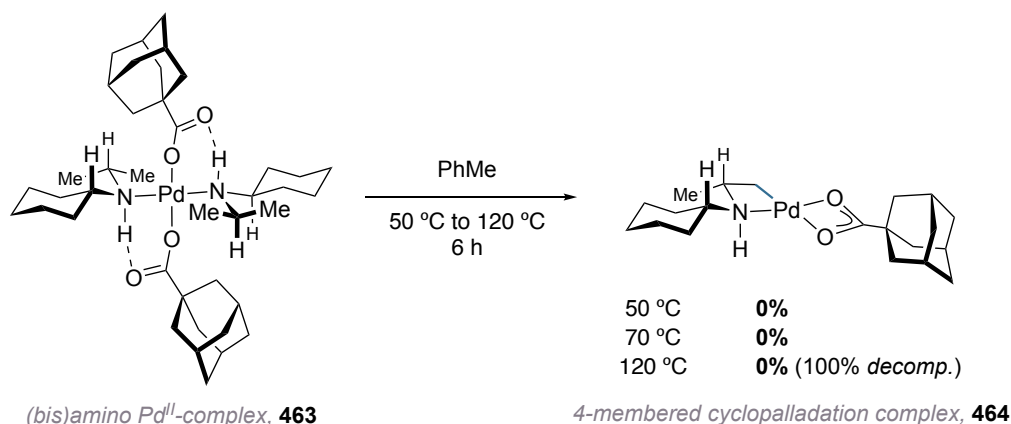
### 2.1 Previous work

Seminal work presented in 2014 demonstrated that hindered TMP-derived secondary amines underwent 4-membered ring cyclopalladation/1,1-migratory into CO to form an acyl–Pd species, which subsequently underwent reductive elimination to generate β-lactam products **298** (Scheme 67)<sup>337</sup>. However, when the same reaction was applied to more commonly encountered less-hindered amines bearing α-hydrogens, the corresponding β-lactams **459** were obtained in dramatically lower yields (Figure 2a).



**Figure 2** | (a) Pd-Catalyzed carbonylation of alkylamines. (b) Observed decomposition products

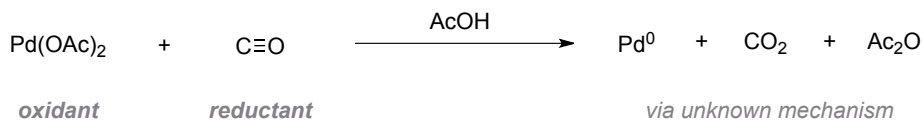
Early work by Dr D. Willcox revealed that the carbonylation of *N*-isopropylcyclohexylamine (**471**, Scheme 99) generated substantial amounts of decomposition products: imine and hydrolysis products resulting from β-hydride elimination **460**; oxidation by-products including *N*-isopropylaniline and phenol, presumably stemming from sequential Saegusa-type oxidations **461**<sup>428</sup>; as well as the acetylated amine **462** (Figure 2b). Moreover, attempts by Dr D. Willcox and Dr B. Chappell to observe any four-membered ring cyclopalladation complexes **464** were unfruitful, instead the bis(amino) Pd<sup>II</sup>-complexes **463** were found to undergo decomposition at elevated temperatures (Scheme 95). Taken together, these results indicated that a new non-classical mechanism for C–H carbonylation could be operating. In 2016, Gaunt subsequently outlined a general strategy for the β-C–H carbonylation of less-hindered aliphatic amines to form β-lactams<sup>429</sup>.



**Scheme 95** | Attempted 4-membered ring stoichiometric cyclopalladation. Reactions conducted independently by Dr D. Willcox and Dr B. Chappell

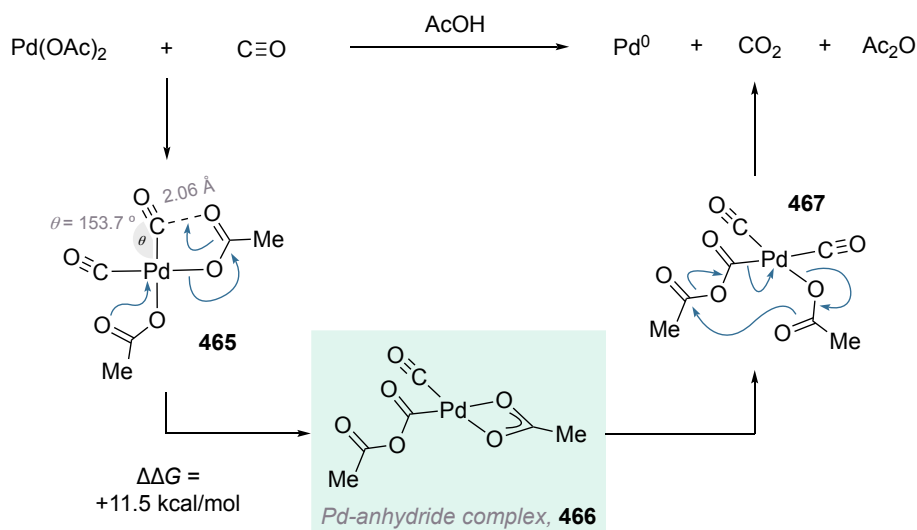
Perhaps unsurprisingly, the strongly reducing properties of CO and the oxidative nature of Pd(OAc)<sub>2</sub> are intrinsically incompatible, predictably leading to catalyst reduction and eventually deactivation. Intriguingly, a significant number of carbonylation technologies are founded upon the combination of these reagents, though paradoxically, little is known about the mechanism of their reaction. Limited reports by Moiseev in the early 1980's identified that the reaction of Pd(OAc)<sub>2</sub> and CO generated Pd<sup>0</sup>, CO<sub>2</sub>, and Ac<sub>2</sub>O, although no mechanistic insight was provided and little evidence of any intermediates (Scheme 96)<sup>430,431</sup>.

Moiseev (1983)



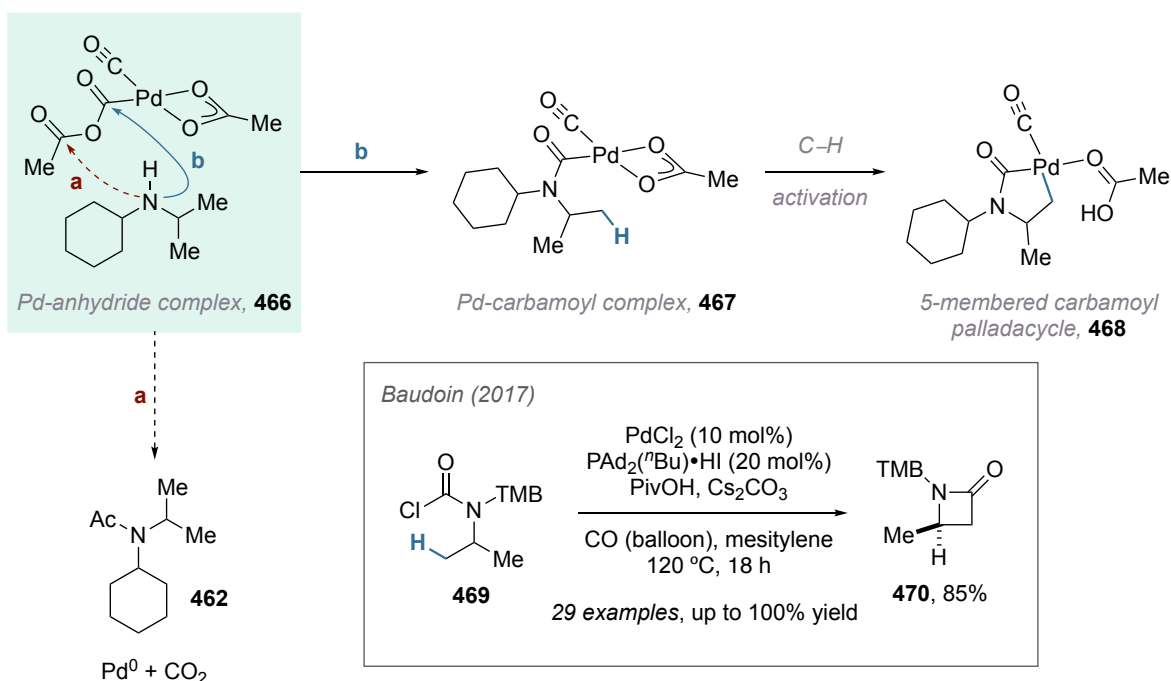
**Scheme 96** | Decomposition of palladium(II) acetate by carbon monoxide

Computational studies by Dr B. Chappell on a simplified model system identified that coordination of two molecules of CO to Pd(OAc)<sub>2</sub> furnishes a square planar intermediate **465**; interestingly, the Pd–C–O bond angle was found to be  $\theta = 153.7^\circ$  and the CO–OAc bond distance 2.06 Å, indicating a significant interaction between the acetate oxygen lone pair and carbonyl  $\pi^*$ -orbital (Scheme 97)<sup>432</sup>. Accordingly, migration of the CO ligand by the neighbouring carboxylate was found to be energetically favourable, leading to an unusual Pd-anhydride species **466** ( $\Delta\Delta G = +11.5$  kcal/mol). It was proposed that intramolecular attack of the remaining  $\kappa^1$ -bound acetate to the distal carbonyl of the anhydride **467** would generate Ac<sub>2</sub>O, CO<sub>2</sub> and Pd<sup>0</sup>, in line with the observations of Moiseev.

computed CO mediated decomposition of  $Pd(OAc)_2$  (Dr B. Chappell)

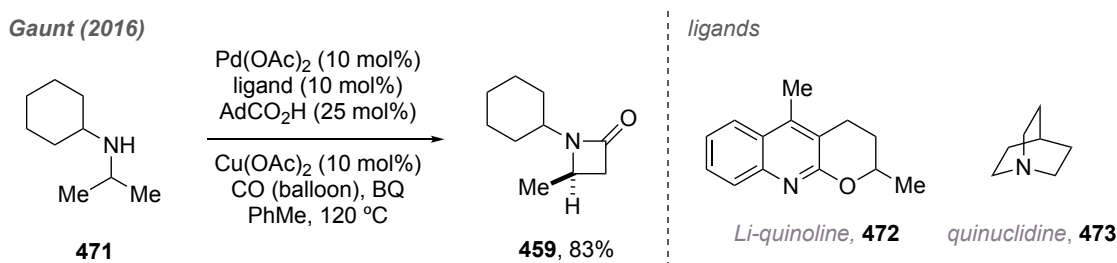
**Scheme 97** | Computed decomposition pathway for palladium(II) acetate by carbon monoxide. DFT calculations performed using ADF/BLYP-D3/TZ2P

In the context of amine C–H carbonylation, it was questioned that if an alkylamine attacked the Pd-anhydride species *in lieu* of the bound acetate, could the resulting species be harnessed productively for C–H activation. Ostensibly, there are two electrophilic positions of the Pd-anhydride **466** that an amine could attack: (a) the distal carbonyl, which would result in acetylation of the amine **462** with loss of  $CO_2$  and the formation of  $Pd^0$ ; and (b) the proximal carbonyl, leading to a Pd-carbamoyl complex **467** (Scheme 98). It was considered that such a Pd-carbamoyl could undergo C–H activation to form a 5-membered carbamoyl palladacycle **468**, after which, reductive elimination would provide the  $\beta$ -lactam product. Early work by Takemoto<sup>433</sup> and more recently by Baudoin (Scheme 98)<sup>434</sup> has exploited similar species for Pd-catalyzed C–H activation generated via the oxidative addition of  $Pd^0$  to carbamoyl chlorides **469**, leading to the formation of  $\beta$ -lactams **470**.



**Scheme 98** | Possible reaction pathways for a putative  $\text{Pd}$ -anhydride complex with alkylamines

In order to promote addition to the proximal carbonyl of the anhydride, it was hypothesized that by utilizing a sterically encumbered carboxylic acid, unproductive attack of the distal carbonyl adjacent to the steric bulk would be diminished. Gratifyingly, addition of catalytic adamantanoic acid ( $\text{AdCO}_2\text{H}$ ) to the standard reaction conditions resulted in an improvement in the yield of the  $\beta$ -lactam product **459** (32%). Moreover, a similarly beneficial effect was found upon the addition of 1,4-benzoquinone (BQ) (**319**, Scheme 70), a strong  $\pi$ -acid, by promoting reductive elimination of the product from  $\text{Pd}^{\text{II}}$  (*vide infra*). Importantly, the combination of these two reagents was found to be additive, resulting in a dramatic increase in the yield (65%). Further studies revealed that the addition of nitrogen based Li-quinoline **472** and quinuclidine **473** ligands allowed the loading of other components to be decreased; the ligands presumably acting as scavengers for  $\text{Pd}^0$  by preventing agglomeration and eventual catalyst death (Scheme 99).

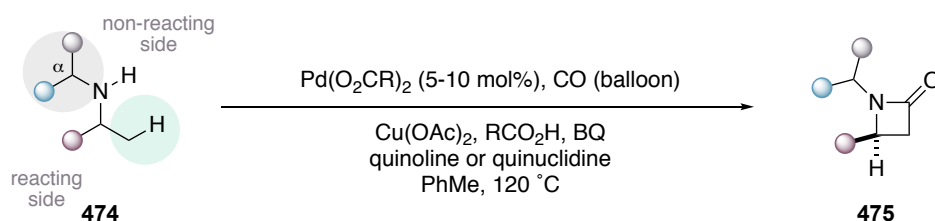


**Scheme 99** | Optimized conditions for the  $\text{Pd}$ -catalyzed carbonylation of less-hindered alkylamines

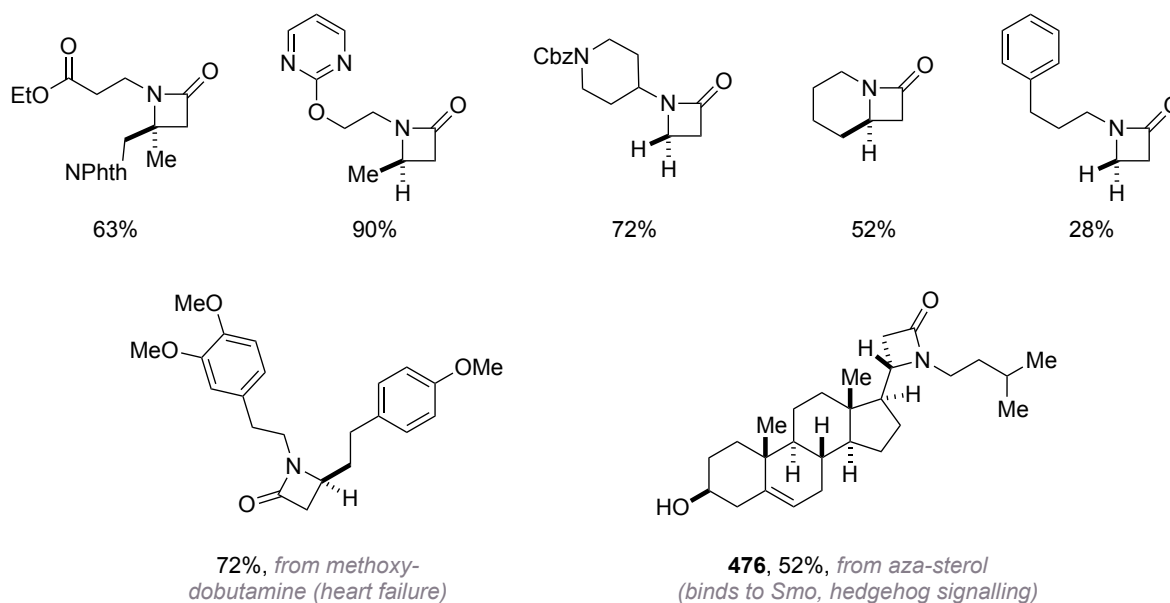
With optimal conditions in hand, the scope of C–H carbonylation was investigated across all classes of substituted secondary alkylamines **474** (Scheme 100). Pleasingly the reaction proved remarkably



general, tolerating a wide variety of functional groups including thioethers, pendant alkenes and Lewis basic heterocycles – groups known to poison Pd-catalysts<sup>435</sup>. Alkylamines bearing one  $\alpha$ -H through to four  $\alpha$ -H's were well-tolerated, forming a range of  $\beta$ -lactams **475** in moderate to good yields (up to 90% yield). Impressively, a series of more complex pharmaceuticals underwent C–H carbonylation in good yields, most notably aza-Sterol **476** containing an unprotected alcohol, without competing Uemura-type oxidation<sup>436</sup>.

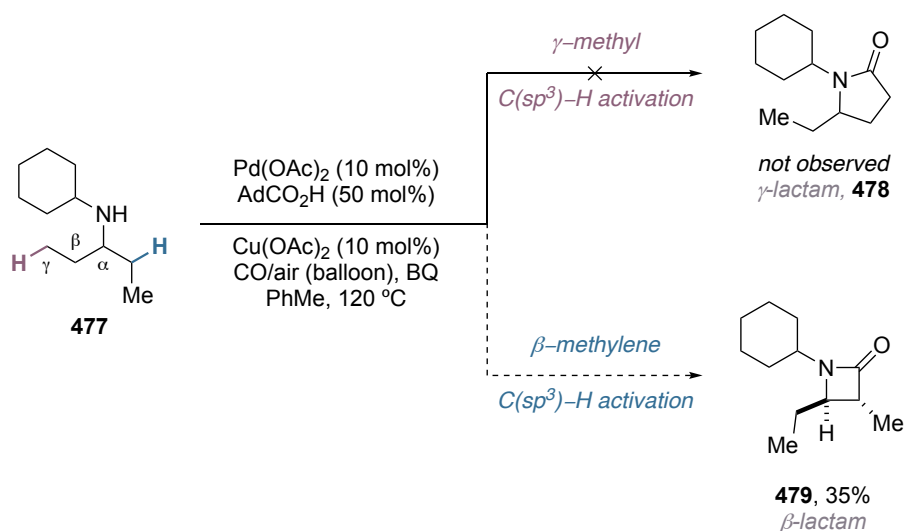


example substrates (Gaunt, 2016)



**Scheme 100** | Scope of Pd-catalyzed carbonylation of alkylamines. R = Me or 2,4,6-mesityl.

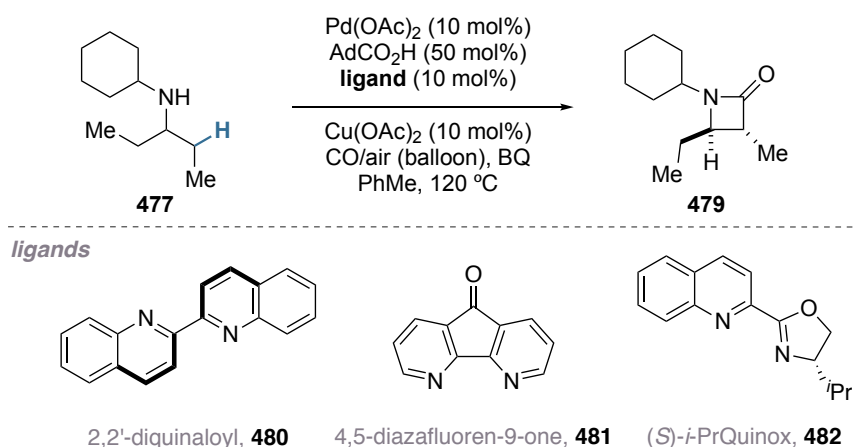
During the early stages of this investigation, an important test substrate, *N*-(pentan-3-yl)cyclohexylamine **477**, was examined by Dr K. Ozaki with anticipation that 6-membered ring cyclopalladation of the carbamoyl Pd-species would occur, furnishing the corresponding  $\gamma$ -lactam product **478** (Scheme 101).



**Scheme 101** | Pd-catalyzed carbonylation of *N*-(pentan-3-yl)cyclohexylamine

Remarkably however, a  $\beta$ -lactam **479** was obtained as a single diastereoisomer resulting from activation of the  $\beta$ -methylene C–H bond in preference to the  $\gamma$ -methyl C–H bond. Moreover, activation occurred exclusively on the acyclic 3-pentyl group. Due to increased sterics around the C–H activation and reductive elimination transition states, the activation of mid-chain methylene C–H bonds is challenging, often requiring strongly-coordinating auxiliaries<sup>261</sup>. What's more, the activation of diastereotopic methylene C–H bond often occurs with little stereocontrol, regularly leading to mixtures of products<sup>437</sup>. To the best of our knowledge, this unusual result constitutes the first example of methylene C–H bond functionalization in the  $\beta$ -position to an unprotected aliphatic amine; importantly, such a transformation gives rise to functionally diverse and biologically relevant complex  $\beta$ -lactam products<sup>438,439</sup>.

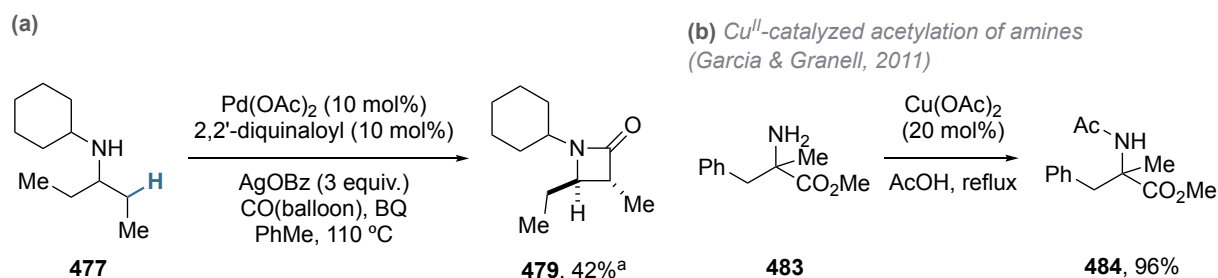
Early optimization studies by Dr K. Ozaki identified that the addition of (*S*)-*i*PrQuinox **482** as a ligand improved the yield of the  $\beta$ -lactam product **479** substantially (65%, by <sup>1</sup>H NMR) (Table 1, entry 4). Along these lines, similar 2,2'-diquinoloyl **480**, azafluorenone **481** and 2,2'-bipyridine ligands also proved effective, affording the product in a 57%, 47% and 54% yield respectively (Table 1, entries 1–3). Markedly, Yu has reported that similar quinoline based ligands are crucial in facilitating the methylene C–H arylation of electron-deficient *N*-arylamides<sup>261</sup>.



Entry	Ligand	Yield (%) <sup>a</sup>
1	bpy	54
2	2,2'-diquinaloyl	57
3	4,5-diazafluoren-9-one	47
4	(S)-i-PrQuinox	65

**Table 1** | Early optimization studies for methylene  $\beta$ -C( $sp^3$ )–H activation of *N*-(pentan-3-yl)cyclohexylamine. Reactions conducted by Dr K. Ozaki. <sup>a</sup>Yields determined by  $^1H$  NMR against internal standard 1,1,2,2-tetrachloroethane.

Despite this early success, continuation of the project by Dr J. Cabrera-Pardo was met with poor reproducibility, in fact, only 2,2'-diquinaloyl was found to generate the product under the reaction conditions in a 13% yield. Detailed analysis of the crude reaction mixture led to the discovery that large amounts of *N*-acetylated by-products were being formed under the reaction conditions. Garcia and Granell have demonstrated that  $Cu^{II}$  salts can catalyze the *N*-acetylation (**484**) of amines **483** in  $Pd$ -mediated carbonylation reactions via the formation of acetic anhydride (*vide supra*) (Scheme 102b). Therefore, changing the oxidant from  $Cu(OAc)_2$  to  $AgOBz$  increased the yield to 42% with consistent reproducibility (Scheme 102a).

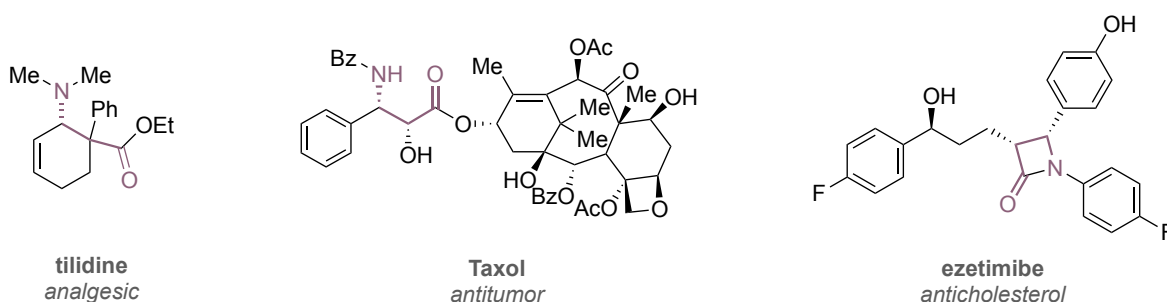


**Scheme 102** | (a)  $Pd$ -catalyzed carbonylation employing  $Ag$  co-oxidant (Dr J. Cabrera-Pardo). (b)  $Cu$ -catalyzed acetylation of amines

## 2.2 Project aims

Over the last twenty years, the advent of transition metal-mediated C–H activation processes has resulted in a step-change in synthetic chemistry. While the majority of these transformations embrace

bespoke functional groups to drive this transformation, the use of native directing groups remains challenging. Moreover, the selective functionalization of mid-chain C–H bonds is hampered by increased steric interactions. Despite recent intensive efforts by Dong<sup>332</sup>, Ge<sup>333</sup> and Yu<sup>334</sup>, the majority of auxiliary-controlled methylene C–H bond activation processes take place at the  $\gamma$ -position to the amine by classical five-membered ring cyclopalladation. To the best of our knowledge, there are currently no direct functionalization processes that selectively target a methylene C–H bond in the  $\beta$ -position to an unprotected alkylamine, such a process would give rise to a structural motif present in a wide-array of biologically relevant complex amines (Figure 3)<sup>440,441</sup>.



**Figure 3** | Importance of  $\beta$ -functionalized amines

The goal of this project is to optimize and develop a general platform for the methylene  $\beta$ -C–H bond functionalization of alkylamines. Building upon the recently elucidated mechanistic pathway for amine carbonylation, we aim to overcome the constraints of classical cyclopalladation via a novel Pd-carbamoyl intermediate in order to generate disubstituted  $\beta$ -lactam products in high yields and excellent diastereoselectivities.

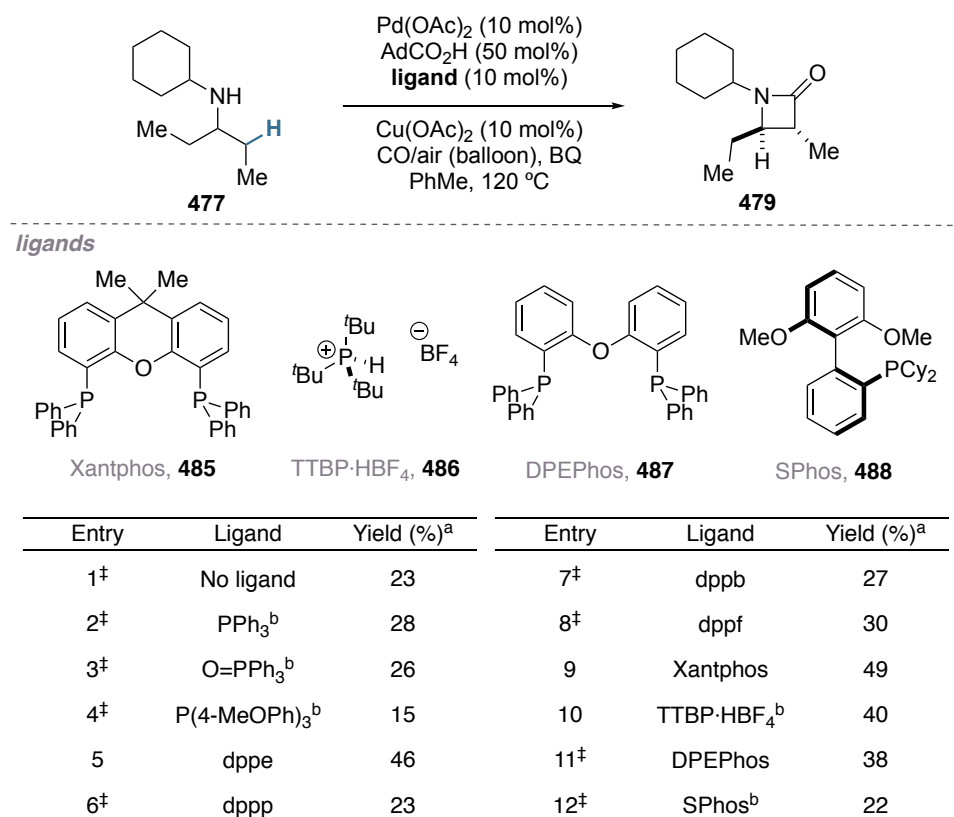
We endeavoured to explore the functional group compatibility and selectivity of the transformation in order to realize a methodology capable of discriminating between different methylene  $\beta$ -C–H bonds. In addition, we sought to demonstrate the utility of such a process via further functional group manipulation of the  $\beta$ -lactam products as well as undertake preliminary mechanistic investigations.

Due to the collaborative nature of this project, for clarity, all work undertaken is attributed by name both within the text and schemes.

### 2.3 Results and discussion

With initial optimization results in hand, attention was turned to screening alternative ligand classes with Dr J. Cabrera-Pardo. Phosphines ligands have been used extensively in both Pd-catalyzed carbonylation<sup>442,443</sup> and C–H activation reactions<sup>444–450</sup>. Arguably, their structural diversity, unique

stereoelectronic properties and commercial availability have rendered them the most important ligand class in transition metal catalysis<sup>451,452</sup>. As such, a series of mono- and bidentate phosphine-derived ligands were trialled under the reaction conditions.



**Table 2** | Phosphine ligands for Pd-catalyzed amine carbonylation. <sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane. <sup>b</sup>Conducted using 20 mol% ligand. <sup>‡</sup>Reaction conducted by Dr J. Cabrera-Pardo

From these results, it was apparent that triphenylphosphine and triphenylphosphine oxide had little effect on the reaction outcome (Table 2, entries 2 and 3) compared to the control reaction without ligand (Table 2, entry 1). Interestingly, the more electron-rich tri(4-methoxyphenyl)phosphine seemingly retarded the reaction, presumably due to unfavourable electronics concerning the reductive elimination (Table 2, entry 4)<sup>453</sup>.

Both Hartwig and Buchwald have reported that bidentate ligands can prevent deleterious  $\beta$ -hydride elimination by virtue of their larger coordination sphere<sup>454,455</sup>. Further work by Spencer and Orpen detailed that the effect was magnified upon increasing bite-angle<sup>456</sup>. Moreover, large bite angle bidentate phosphine ligands have been shown to promote reductive elimination from  $\text{Pd}^{\text{II}}$  species<sup>457,458</sup>. In this manner, dppe, Xantphos **485** and DPEPhos **487** showed significant enhancements to the yield, furnishing the  $\beta$ -lactam product **479** in 46%, 38% and 49% respectively (Table 2, entries 5, 9 and 11). However, dppp, dppb and DPPF homologues failed to have any appreciable effect on the yield, potentially due to oxidative instability under the reaction conditions

(Table 2, entries 6–8). Along these lines, Buchwald ligand SPhos **488** proved similarly ineffective, affording the product in a 22% yield (Table 2, entry 12).

At the same time, a series of mono- and bidentate pyridine ligands were tested under the reaction conditions by Dr J. Cabrera-Pardo<sup>459</sup>. Although 4-*tert*-butylpyridine had little effect on the yield (Table 3, entry 2), more sterically demanding 2,6-lutidine proved more fruitful (Table 3, entry 1), delivering the product **479** in a 42% yield. In line with these findings, bulkier Li-quinoline **472** and Li-Yu *tert*-butylquinoline **489** ligands gave similarly improved yields, 51% and 52% respectively (Table 3, entries 3 and 4). Unsurprisingly, hindered 2,6-di-*tert*-butylpyridine had no impact on the reaction compared with the control in the absence of ligand (Table 3, entry 6). Strongly σ-donating bidentate Me<sub>4</sub>Phen **490** and BBBPy **491** ligands exhibited near complete reaction inhibition, most likely due to saturation of the catalyst active sites (Table 3, entries 5 and 7).

**477**

Pd(OAc)<sub>2</sub> (10 mol%)  
 AdCO<sub>2</sub>H (50 mol%)  
**ligand** (10 mol%)  
 Cu(OAc)<sub>2</sub> (10 mol%)  
 CO/air (balloon), BQ  
 PhMe, 120 °C

**479**

### ligands

R<sup>1</sup> = H, Li-quinoline, **472**

R<sup>1</sup> = *t*-Bu, Li-Yu *t*-Bu-quinoline, **489**

Me<sub>4</sub>Phen, **490**

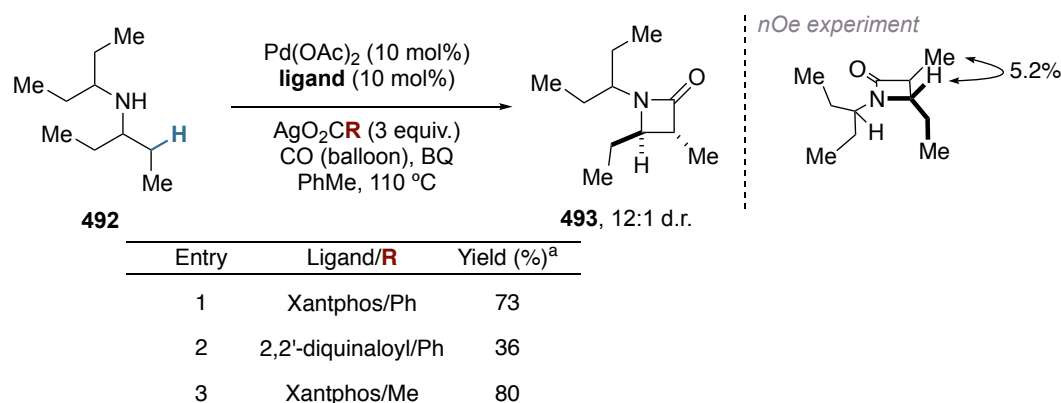
BBBPy, **491**

Entry	Ligand	Yield (%) <sup>a</sup>	Entry	Ligand	Yield (%) <sup>a</sup>
1 <sup>‡</sup>	2,6-lutidine	42	5	BBBPy	8
2 <sup>‡</sup>	4- <i>t</i> -Bu-pyridine	25	6 <sup>‡</sup>	2,6-di- <i>t</i> -Bu-pyridine	28
3 <sup>‡</sup>	Li-quinoline	51	7 <sup>‡</sup>	Me <sub>4</sub> Phen	trace
4 <sup>‡</sup>	Li-Yu <i>t</i> -Bu-quinoline	52			

**Table 3** | Pyridine ligands for Pd-catalyzed amine carbonylation. <sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane. <sup>‡</sup>Reaction conducted by Dr J. Cabrera-Pardo

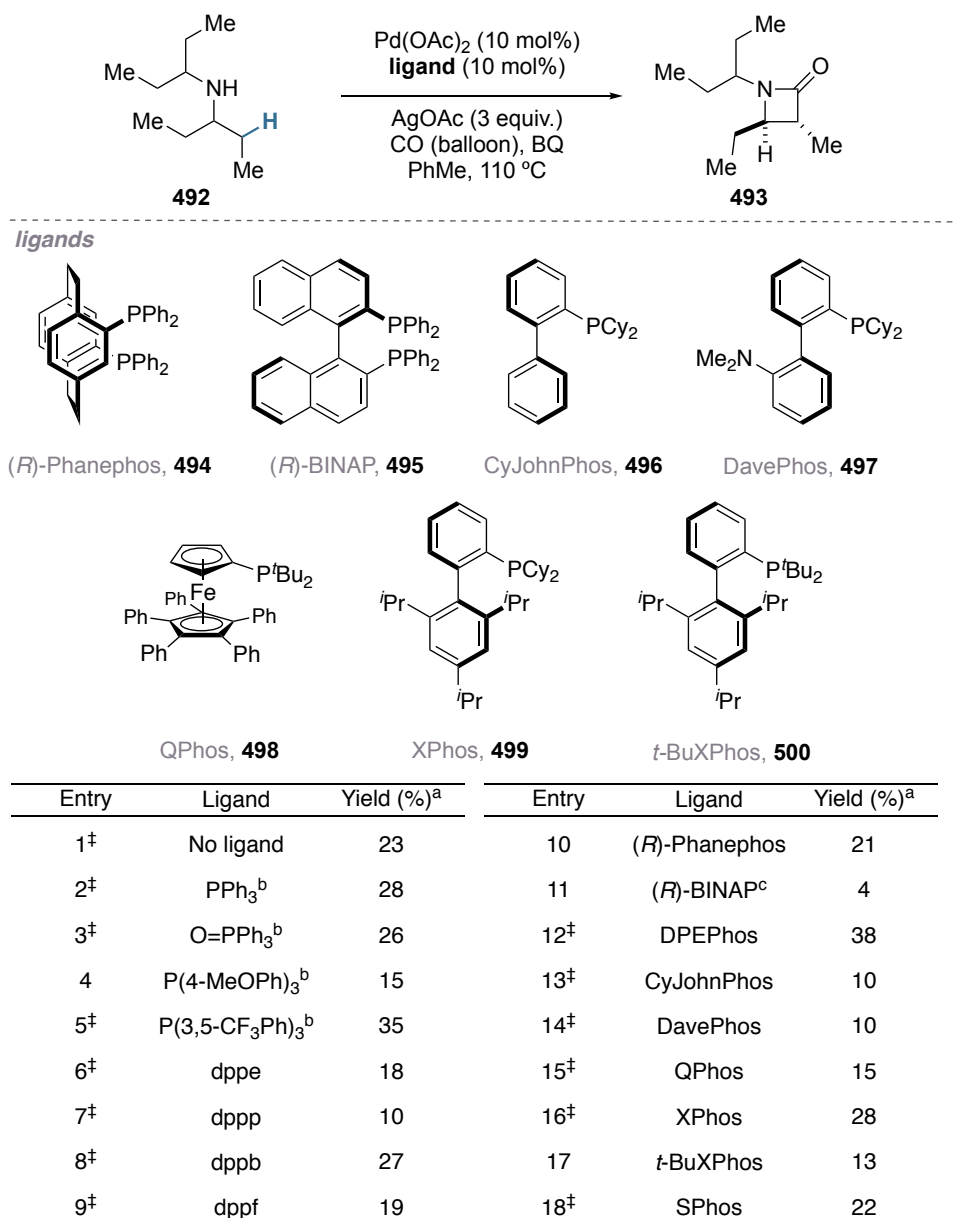
As a result of these screens, both Xantphos **485** and 2,2'-diquinoloyl **480** were chosen as representative ligands from each class for further parameter optimization including catalyst/ligand loading, solvents, oxidants and the addition of additives (*see* Appendix II, tables 24–27). Regrettably, no significant improvement to the yield of β-lactam **479** above 60% could be achieved; therefore, it was reasoned that an alternative amine might be more susceptible to the desired transformation.

Symmetrical di(pentan-3-yl)amine **492** was chosen as the archetypical substrate due to the four equivalent  $\beta$ -methylene C–H bond environments. Upon subsection of the amine to the reaction conditions using Xantphos **485** as a ligand, the  $\beta$ -lactam product **493** was obtained in 73% yield (12:1 d.r.) (Table 4, entry 1). Surprisingly, using 2,2'-diquinoloyl **480** as the ligand furnished the  $\beta$ -lactam **493** in a lower 36% yield (Table 4, entry 2). Furthermore, exchanging AgOBz for AgOAc led to further improvement in the yield to 80% (Table 4, entry 3). Selective nOe experiments established that the stereochemistry of the major  $\beta$ -lactam diastereoisomer was *trans*-substituted<sup>460</sup>.



**Table 4** | Ligand effects for the Pd-catalyzed carbonylation of di(pentan-3-yl)amine. <sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane.

Given the, seemingly, non-uniform ligand effect between the amine substrates, a further optimization study was undertaken with Dr J. Cabrera-Pardo. The reaction proceeded poorly in the absence of any ligand, delivering the product **493** in a 23% yield (Table 5, entry 1). Similarly, both triphenylphosphine and triphenylphosphine oxide exhibited negligible effects (Table 5, entries 2 and 3). In agreement with previous ligand screens, electron-rich tri(4-methoxyphenyl)phosphine gave rise to a lower yield of the product (Table 5, entry 4). Although a small increase in yield (35%) was observed using electron-poor tri(3,5-bis(trifluoromethyl)phenyl)phosphine (Table 5, entry 5), the effect was negligible compared with the standard conditions. Bis(diphenylphosphino)alkanes and Phanephos **494** ligands had little positive effect on the reaction, in the majority of cases returning the product **493** in diminished yields compared to the control reaction in the absence of ligand (Table 5, entries 6–10). The addition of BINAP **495** as a ligand effectively shut down the reaction, presumably due to the strong bidentate chelation removing the vacant sites required for C–H activation to occur (Table 5, entry 11). The more flexible Xantphos analogue DPEPhos **487** gave only a modest increase in yield (Table 5, entry 12), affording the  $\beta$ -lactam product **493** in 38% yield compared to the control reaction. Once again, a survey of Buchwald ligands (**488**, **496–500**) resulted in low conversion of the amine to the  $\beta$ -lactam product **493** (Table 5, entries 13–18).

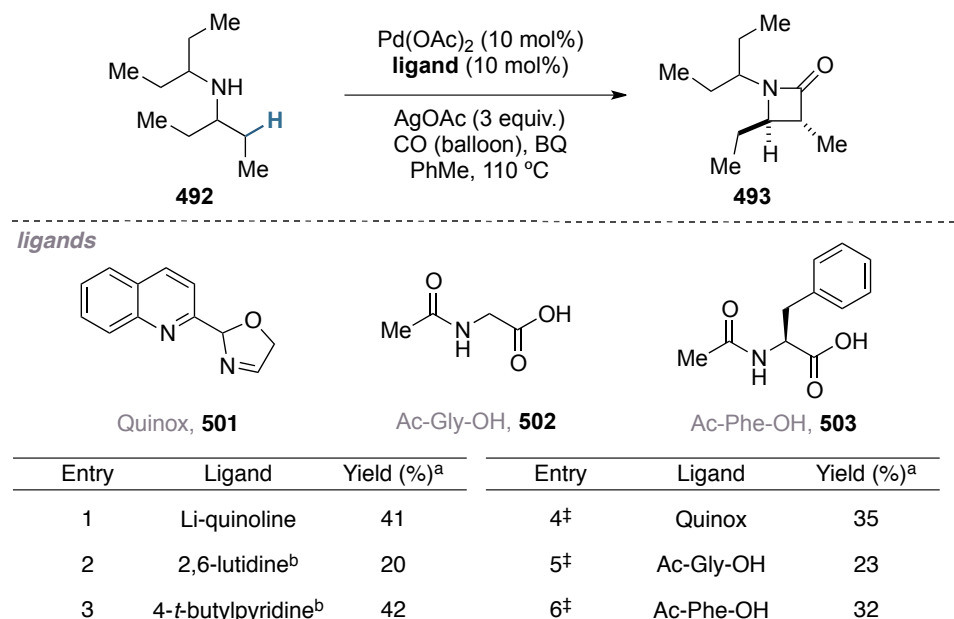


**Table 5** | Phosphine ligands for Pd-catalyzed amine carbonylation of di(pentan-3-yl)amine. <sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane. <sup>b</sup>Conducted using 20 mol% ligand. <sup>‡</sup>Reaction conducted by Dr J. Cabrera-Pardo

Although similar improvements to the yield were observed using both Li-quinoline **472** and Xantphos **485** ligands for the C–H carbonylation of *N*-(pentan-3-yl)cyclohexylamine **477**, this was not the case with di(pentan-3-yl)amine **492**. While Li-quinoline and 4-*tert*-butylpyridine showed a moderate enhancement, affording the β-lactam product **493** in 41% and 42% yield respectively (Table 6, entries 1 and 3), 2,6-lutidine and Quinox **501** showed little improvement (Table 6, entries 2 and 4). Moreover, mono-protected amino acid (MPPA) ligands **502** and **503**, previously used for aliphatic amine C–H activation<sup>307</sup>, offered little enhancement to the yield (Table 6, entries 5 and 6). Other ligand classes including thioureas and NHCs, which have been shown to be proficient ligands

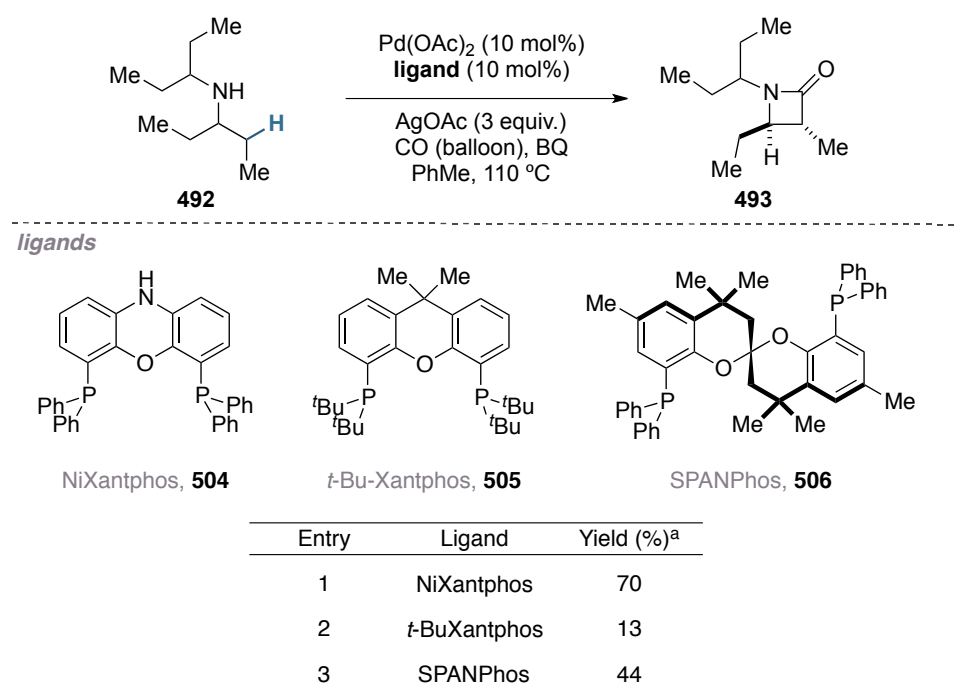


for Pd-catalyzed carbonylation were also screened<sup>461</sup>; however, no improvements to the yield were observed (see Appendix II, table 28).



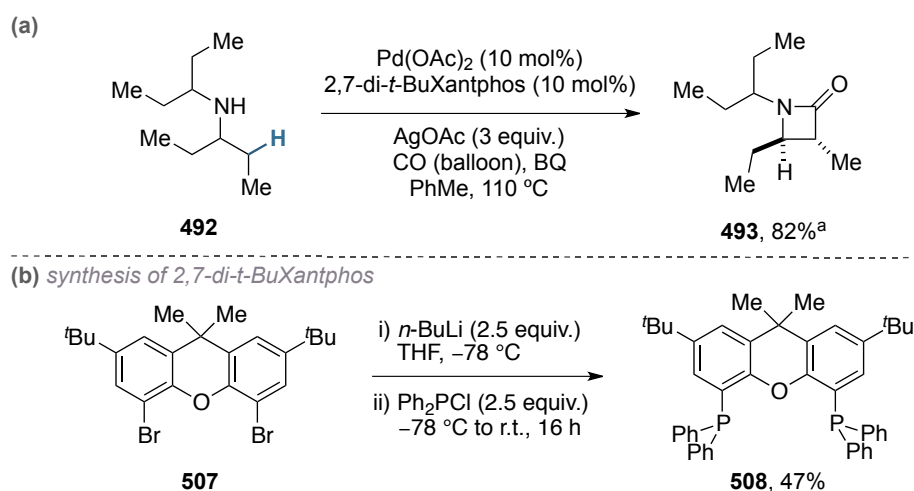
**Table 6** | Pyridine and amino acid ligands for Pd-catalyzed amine carbonylation of di(pentan-3-yl)amine. <sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane. <sup>b</sup>Conducted using 20 mol% ligand. <sup>‡</sup>Reaction conducted by Dr J. Cabrera-Pardo

Given the apparent importance of the Xantphos backbone, a series of analogues were tested<sup>462</sup>. Commercial phenoxazine-derived NiXantphos **504** performed similarly to the parent Xantphos ligand, affording the product **493** in 70% yield (Table 7, entry 1).



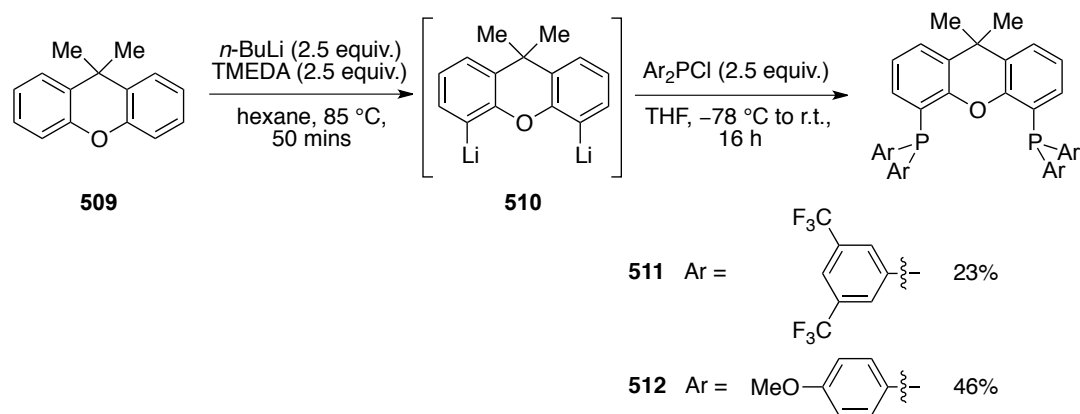
**Table 7** | Xantphos-derived ligands for the Pd-catalyzed carbonylation of di(pentan-3-yl)amine. <sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane

However, di-*tert*-butylXantphos **505** performed particularly poorly, furnishing the  $\beta$ -lactam **493** in a 13% yield (Table 7, entry 2). It is believed that the oxidative sensitivity of the dialkylphosphine may lead to rapid formation of the bis-phosphine oxide under the reaction conditions. The extreme flexibility of Xantphos (bite angle:  $\theta = 99^\circ$  to  $164^\circ$ ) has resulted in the observation of both *cis*- and *trans*-spanning binding modes<sup>463</sup>; therefore, the larger bite angle SPANPhos ligand **506** (P–Pt–P,  $\theta = 171.9^\circ$ ) was investigated<sup>464</sup>. Unfortunately, the desired  $\beta$ -lactam product **493** was produced in a diminished 44% yield (Table 7, entry 3). In addition, the more soluble 2,7-di-*tert*-butylXantphos **508** reported by Buchwald was prepared by lithium-halogen exchange of 4,5-dibromo-2,7-di-*tert*-butyl-9,9-dimethylxanthene **507** and quenching with diphenylchlorophosphine in a 47% yield (Scheme 103b)<sup>465</sup>. The ligand performed comparatively well under the reaction conditions, affording the product **493** in an 82% yield (Scheme 103a).



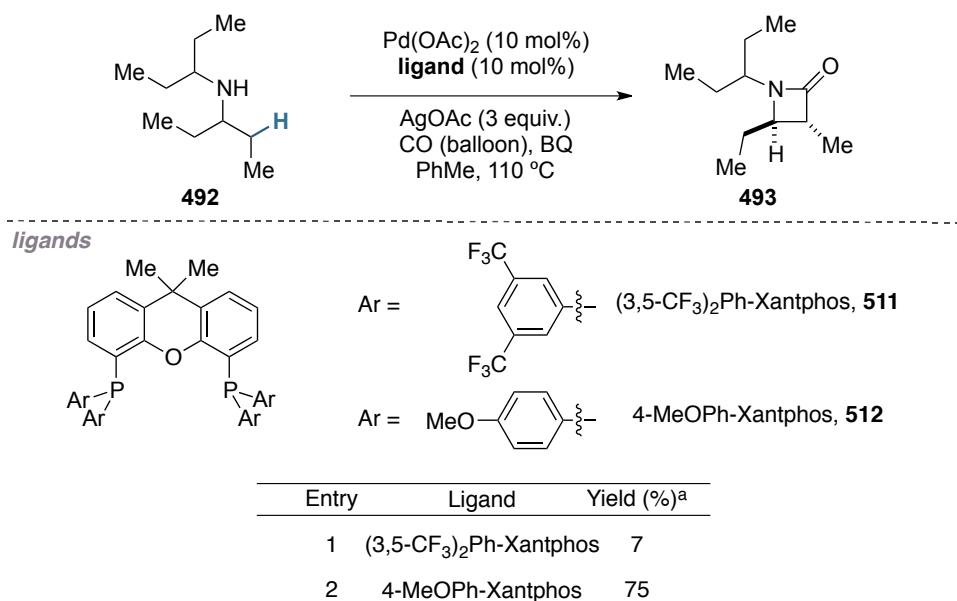
**Scheme 103** | (a) Evaluation of 2,7-di-*tert*-butylXantphos as a ligand for the Pd-catalyzed carbonylation of di(pentan-3-yl)amine. (b) Ligand synthesis. <sup>a</sup>Yield determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane

As the electronic properties of the phosphine ligands have been shown to affect the yield, electron-rich and electron-deficient Xantphos analogues were prepared in a similar manner to that reported by Beletskaya (Scheme 104)<sup>466</sup>. The selective dilithiation of 9,9-dimethylxanthene **509** afforded the 4,5-dilithiated intermediate **510**, which was subsequently quenched with the appropriate diarylchlorophosphine. The electron-deficient 3,5-(CF<sub>3</sub>)<sub>2</sub>Ph-Xantphos derivative **511** was synthesized in an overall 23% yield, and the corresponding electron-rich 4-OMePh-Xantphos **512** in an improved 46% yield.



**Scheme 104** | Preparation of electronically distinct Xantphos ligands

Interestingly, when subjected to the reaction conditions, electron-deficient 3,5-( $\text{CF}_3$ )<sub>2</sub>Ph-Xantphos **511** severely impeded the reaction, forming the  $\beta$ -lactam product **493** in a 7% yield, contrary to the remedial electronic effect exhibited by [3,5-( $\text{CF}_3$ )<sub>2</sub>Ph]<sub>3</sub>P (Table 8, entry 1). Furthermore, 4-OMePh-Xantphos **512** behaved similarly to the parent Xantphos ligand, generating the product **493** in a slightly reduced 75% yield (Table 8, entry 2). Taken together, it was reasoned that a subtler ligand effect might be operating under the reaction conditions.

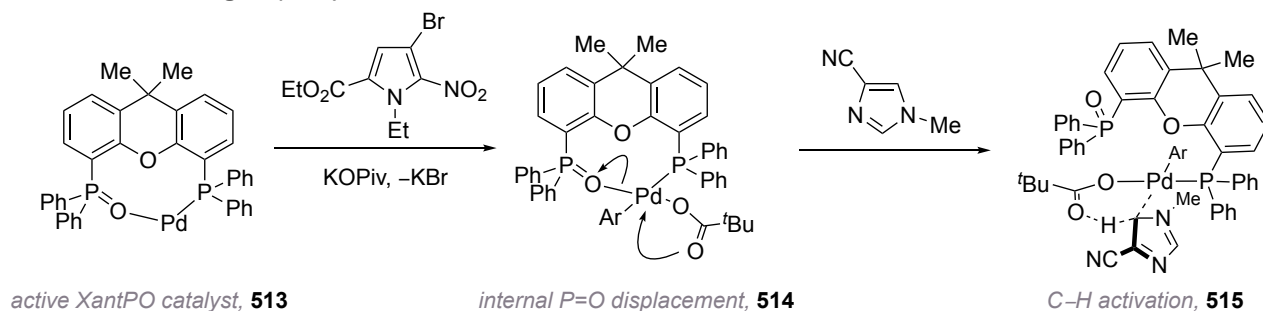


**Table 8** | Evaluation of Xantphos-derived ligands for the Pd-catalyzed carbonylation of di(pentan-3-yl)amine. <sup>a</sup>Yield determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane

In 2015, Blackmond and Eastgate reported that Xantphos mono oxide **516** (XantPO) was an active ligand for Pd-catalyzed C–H functionalization **515** (Scheme 105)<sup>467</sup>. While Xantphos **485** and XantPO **516** gave similar results, kinetic analysis revealed that the bisphosphine was oxidized *in-situ* to the monoxide by Pd<sup>II</sup> and water **513**. It is proposed that the hemilability of XantPO **516**, i.e. the ability to occupy and vacate reactive sites on the metal centre, was crucial to the success of the

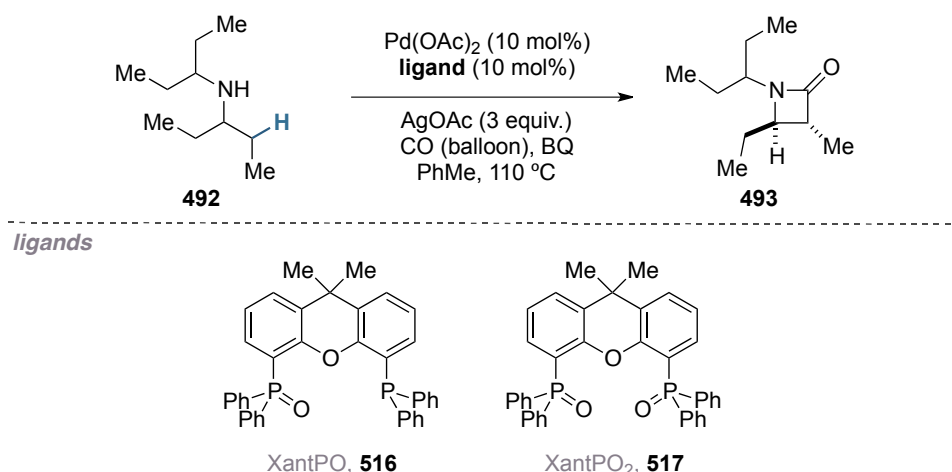
reaction<sup>468</sup>. Dissociation of the weakly bound Pd–O=P bond allows coordination of another molecule of reagent via a low energy pathway **514**.

*Blackmond & Eastgate (2015)*



**Scheme 105** | Xantphos monooxide (XantPO) as a ligand for Pd-catalyzed C–H activation

In order to test whether XantPO **516** was an active catalyst, Dr J. Cabrera-Pardo independently synthesized the ligand and subjected it to the reaction conditions. Remarkably, XantPO **516** afforded the β-lactam product **493** in an 80% yield, identical to that of the parent Xantphos ligand (Table 9, entry 1). It should be noted that Xantphos dioxide (XantPO<sub>2</sub>) **517** generated the product **493** in only a 20% yield, similar to that of the control in the absence of any ligand (Table 9, entry 2).



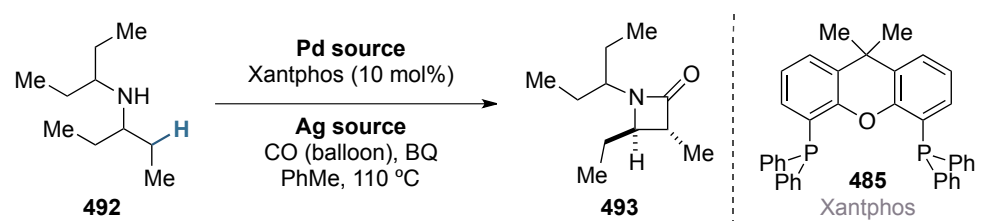
Entry	Ligand	Yield (%) <sup>a</sup>
1 <sup>‡</sup>	XantPO	80
2 <sup>‡</sup>	XantPO <sub>2</sub>	20

**Table 9** | Evaluation of XantPO and XantPO<sub>2</sub> ligands for the Pd-catalyzed carbonylation of di(pentan-3-yl)amine. <sup>a</sup>Yield determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane. <sup>‡</sup>Reaction conducted by Dr J. Cabrera-Pardo

Given the comparable performance between Xantphos and XantPO, we believe that its presence in the active catalyst system is plausible. These findings are in line with the observations made using electron-rich and electron-deficient Xantphos analogues whereby the electron-deficient ligand is unable to undergo efficient oxidation under the reaction conditions. Moreover, the electron-rich ligand may undergo more facile bis-oxidation, furnishing the unreactive bisphosphine dioxide.

However, despite multiple attempts by Dr J. Cabrera-Pardo to observe XantPO in the reaction mixture, only a complex mixture could be observed by  $^{31}P$  NMR (see Appendix II, figures 8–9).

A recent report by Slaughter on Pd-catalyzed C–H amination and arylation revealed that while XantPO **516** was present in the reaction mixture, Xantphos **485** was indeed bound to the catalytically active species<sup>469</sup>. Xantphos's combination of moderate  $\sigma$ -donating ability, wide-bite angle and hemilabile character stabilized by the xanthone oxygen<sup>470</sup>, proving more than sufficient to accommodate inner-sphere CMD and facilitate reductive elimination. Furthermore, recent reports by Denmark<sup>471</sup> and Stahl<sup>472</sup> detailed that phosphine oxides serve as excellent ligands for the stabilization of  $Pd^0$ , competing with CO to prevent the formation of reduced Pd clusters and ultimately Pd black. On balance, we believe that both Xantphos and XantPO may be acting in parallel as ligands during the reaction, their pivotal role most likely stabilizing  $Pd^0$  at the end of the catalytic cycle prior to oxidation back to  $Pd^{II}$ .



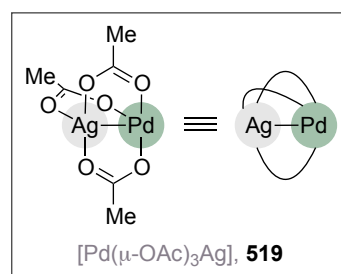
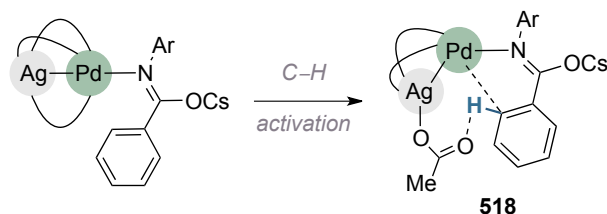
Entry	Palladium (mol %)	Silver (equiv.)	Yield (%) <sup>a</sup>
1	-	AgOAc (3)	0
2	Pd(OAc) <sub>2</sub> (10)	-	N.D.
3 <sup>‡</sup>	Pd(OAc) <sub>2</sub> (5)	AgOAc (3)	47
4 <sup>‡</sup>	PdCl <sub>2</sub> (10)	AgOAc (3)	31
5 <sup>‡</sup>	Pd(TFA) <sub>2</sub> (10)	AgOAc (3)	62
6 <sup>‡</sup>	Pd(OPiv) <sub>2</sub> (10)	AgOAc (3)	44
7	[PdCl <sub>2</sub> (Xantphos)] (10)	AgOAc (3)	77 (82) <sup>‡</sup>
8 <sup>‡</sup>	Pd(OAc) <sub>2</sub> (10)	AgOBz (1)	34
9 <sup>‡</sup>	Pd(OAc) <sub>2</sub> (10)	AgOBz (2)	59
10	Pd(OAc) <sub>2</sub> (10)	AgOBz (3)	70
11	Pd(OAc) <sub>2</sub> (10)	Ag <sub>2</sub> CO <sub>3</sub> (1.5)	trace
12	Pd(OAc) <sub>2</sub> (10)	AgOTf (3)	0
13	Pd(OAc) <sub>2</sub> (10)	Ag <sub>2</sub> O (1.5)	trace
14 <sup>‡</sup>	Pd(OPiv) <sub>2</sub> (10)	AgOPiv (3)	54
15 <sup>‡</sup>	Pd(OBz) <sub>2</sub> (10)	AgOBz (3)	74

**Table 10** | Optimization of Pd and Ag sources for the C–H carbonylation of di(pentan-3-yl)amine. <sup>a</sup>Yields determined by  $^1H$  NMR against internal standard 1,1,2,2-tetrachloroethane. <sup>‡</sup>Reaction conducted by Dr J. Cabrera-Pardo

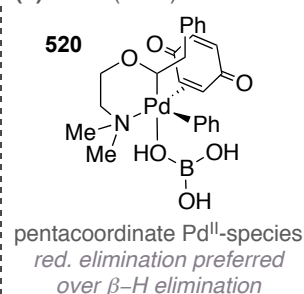
With Xantphos **485** proving the most effective catalyst found to-date, we turned our attention to optimization of the palladium and silver sources. As expected, no product **493** was observed in the absence of Pd(OAc)<sub>2</sub> with the starting amine **492** returned in 77% yield (Table 10, entry 1). Interestingly, in the absence of AgOAc near complete decomposition of the starting amine **492** was observed with only trace of the product observed (Table 10, entry 2). Lowering the catalyst loading to 5 mol% resulted in an appreciable drop in the yield of  $\beta$ -lactam **493** to 47%, with significant quantities of starting amine remaining (Table 10, entry 3). Both Pd(TFA)<sub>2</sub> and Pd(OPiv)<sub>2</sub> performed well under the reaction respectably under the reaction conditions, furnishing the product **493** in a 62% and 44% yield respectively (Table 10, entries 5 and 6). Interestingly, PdCl<sub>2</sub> proved to be somewhat ineffective as a catalyst, generating the product in a lower 31%; however, the pre-formed [Pd(Xantphos)Cl<sub>2</sub>] complex gave almost identical results to the standard reaction, 82%, implicating the potential insolubility of polymeric PdCl<sub>2</sub> in the reaction mixture (Table 10, entries 4 and 7). Diminished yields were obtained upon lowering the equivalents of AgOBz in the reaction, delivering 34% and 59% yield of the product **493** with one and two equivalents respectively (Table 10, entries 8 and 9). Using matching Pd- and Ag-pivalate and -benzoate salts afforded the  $\beta$ -lactam product **493** in 54% and 74% yields (Table 10, entries 14 and 15).

Intriguingly, non-carboxylate-derived Ag salts were not tolerated in the reaction, yielding no  $\beta$ -lactam product **493** and causing decomposition of the starting amine **492** (Table 10, entries 11–13). An interesting report by Sunoj and Schaefer III calculated that [Pd( $\mu$ -OAc)<sub>3</sub>Ag] **519** was the lowest energy active catalyst for C(*sp*<sup>2</sup>)-H activation, wherein CMD occurs from a  $\kappa^1$ -bound [substrate-Pd( $\mu$ -OAc)<sub>2</sub>Ag-OAc] intermediate **518** (Scheme 106a)<sup>473,474</sup>. Although no evidence currently exists to support the intermediacy of a Pd–Ag heterobimetallic species under our reaction conditions, it is clear that the role of AgOAc may be more complex than acting as a simple co-oxidant.

(a) Sunoj & Schaefer III (2014)

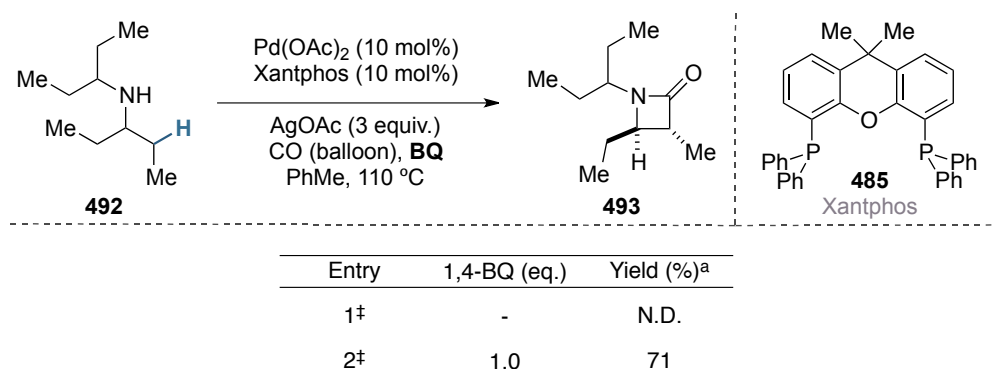


(b) Sköld (2012)



**Scheme 106** | (a) Proposed heterobimetallic Pd–Ag complex for C–H activation. (b) Proposed pentacoordinate Pd<sup>II</sup>-benzoquinone complex

In addition to Pd and Ag sources, the effect of 1,4-benzoquinone (BQ) **319** concentration on the reaction was investigated by Dr J. Cabrera-Pardo. Surprisingly, in the absence of BQ none of the desired  $\beta$ -lactam product **493** was observed, instead significant decomposition of the starting amine **492** was detected (Table 11, entry 1). Simply increasing the amount of BQ **319** to one equivalent had a remarkably curative effect, affording the desired product in a slightly lower 71% yield (Table 11, entry 2). In 2012, Sköld reported that benzoquinone could both suppress  $\beta$ -hydride elimination from  $\text{Pd}^{\text{II}}$ -species as well as facilitate transmetallation and reductive elimination through the formation of pentacoordinate ( $\eta^2$ -BQ) intermediate **520** (Scheme 106b)<sup>475</sup>. Taken together, these findings implicate the role of benzoquinone **319** in promoting the sterically demanding 4-membered ring reductive elimination of the product (*vide supra*) as well as potentially inhibiting deleterious  $\beta$ -hydride elimination. Previous work by Dr K. Ozaki and Dr J. Cabrera-Pardo using *N*-(pentan-3-yl)cyclohexylamine **477** revealed that other quinone derivatives including 1,4-naphthoquinone, anthraquinone as well as various substituted 1,4-benzoquinones performed poorly under the reaction conditions.



**Table 11** | Role of benzoquinone in the Pd-catalyzed C–H carbonylation of di(pentan-3-yl)amine. <sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane. <sup>‡</sup>Reaction conducted by Dr J. Cabrera-Pardo

We next turned our attention towards surveying solvents commonly used in C–H activation. Although reasonable yields of the  $\beta$ -lactam product **493** were observed using  $\text{PhCF}_3$  and 1,2-DCE (65% and 60%) (Table 12, entries 1 and 2), more polar solvents including TFEol, *tert*-BuOH and DMF proved detrimental to the reaction (Table 12, entries 3–7). These observations are in line with the poorer solubility of CO in polar solvents [mole fraction of dissolved CO at 1 atm:  $\text{PhMe}$  ( $X = 8.11 \times 10^{-4}$ ); 1,2-DCE ( $X = 3.88 \times 10^{-4}$ ); DMF ( $X = 1.40 \times 10^{-4}$ )]<sup>476</sup>. Although the addition of carboxylic acids has been shown to increase the yield of Pd-catalyzed C–H activation reactions<sup>477</sup>, little overall effect on the reaction was observed (*see* Appendix II, table 29). Interestingly, the addition of inorganic bases had a significant impact on the efficiency of the reaction, furnishing the  $\beta$ -lactam product **493** in <10% yield (*see* Appendix II, table 29).

Entry	Solvent (Temp °C)	Yield (%) <sup>a</sup>	Entry	Solvent (Temp °C)	Yield (%) <sup>a</sup>
1	CF <sub>3</sub> Ph (85)	65	5	<i>t</i> -BuOH (80)	27
2	1,2-DCE (85)	60	6	DMSO (80)	9
3	TFEol (90)	0	7	DMF (80)	28
4	MeCN (80)	24			

**Table 12** | Role of solvents in the Pd-catalyzed C–H carbonylation of di(pentan-3-yl)amine. <sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane.

In order to ascertain whether any decomposition of the β-lactam product **493** was occurring under the reaction conditions, a time course experiment was undertaken over 16 hours. The results of the time point study suggested that the product **493** is formed rapidly at the start of the reaction, reaching 50% conversion after only 3 hours (Table 13, entry 1). Between 6 and 9 hours, the conversion to product **493** tails off rapidly from 66% to 70% (Table 13, entry 2 and 3), with only an additional 7% conversion seen over the remaining 7 hours (Table 13, entry 4). Pleasingly, no evidence of decomposition was observed over the time period.

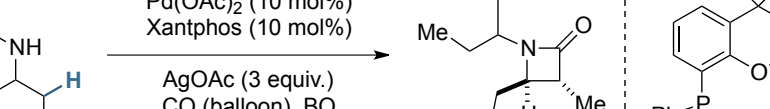
Entry	Time (h)	Yield (%) <sup>a</sup>			
1	3	50			
2	6	66			
3	9	70			
4	16	77			

**Table 13** | Time course studies for the Pd-catalyzed carbonylation of di(pentan-3-yl)amine

The final parameter investigated was the effect of CO concentration on the reaction. Interestingly, when 6.25% CO in air was employed, the β-lactam product **493** was afforded in a diminished 45% yield; however, the formation of the corresponding γ-lactam **521** was observed in 14% yield (Table 14, entry 1). Furthermore, when the concentration of CO was reduced to <2%, the β-lactam product **493** was formed in only 8% yield, yet the γ-lactam **521** was present in a comparable 6% yield (Table 14, entry 2). Mechanistic studies later revealed that an alternative amine γ-



cyclopalladation/carbonylation mechanism could be operating to give the  $\gamma$ -lactam product **521** (*vide infra*). Additional CO sources for “gas-free” carbonylation including  $Mo(CO)_6$  pioneered by Larhed and Odell<sup>478</sup>, as well as the use of COgen apparatus by Skrydstrup<sup>479</sup> were evaluated. Disappointingly, the  $\beta$ -lactam product **493** was returned in significantly reduced yields (Table 14, entries 3 and 4).

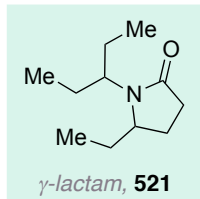


Reaction scheme showing the carbonylation of di(pentan-3-yl)amine (**492**) to  $\beta$ -lactam (**493**) and  $\gamma$ -lactam (**521**).

Reagents:  $\text{Pd}(\text{OAc})_2$  (10 mol%), Xantphos (10 mol%),  $\text{AgOAc}$  (3 equiv.), CO (balloon), BQ, solvent.

Structure of Xantphos (**485**):

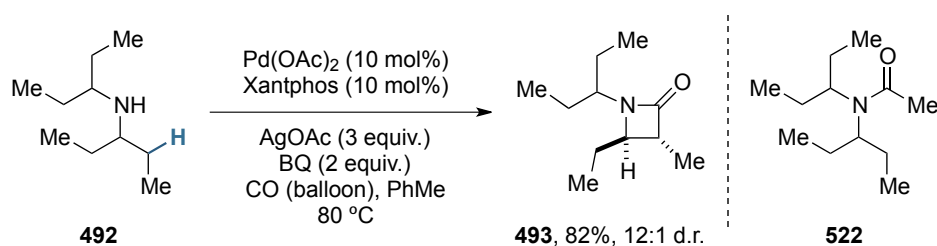
Entry	CO	$\beta$ -lactam (%) <sup>a</sup>	$\gamma$ -lactam (%) <sup>a</sup>
1	6.25% CO in air	45	14
2	> 2% CO in air	8	6
3	$\text{Mo}(\text{CO})_6$	19	-
4 <sup>†</sup>	COgen	14	-



$\gamma$ -lactam, **521**

**Table 14** | Effect of CO concentration for the Pd-catalyzed carbonylation of di(pentan-3-yl)amine. <sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane. <sup>†</sup>Reaction conducted by Dr J. Cabrera-Pardo

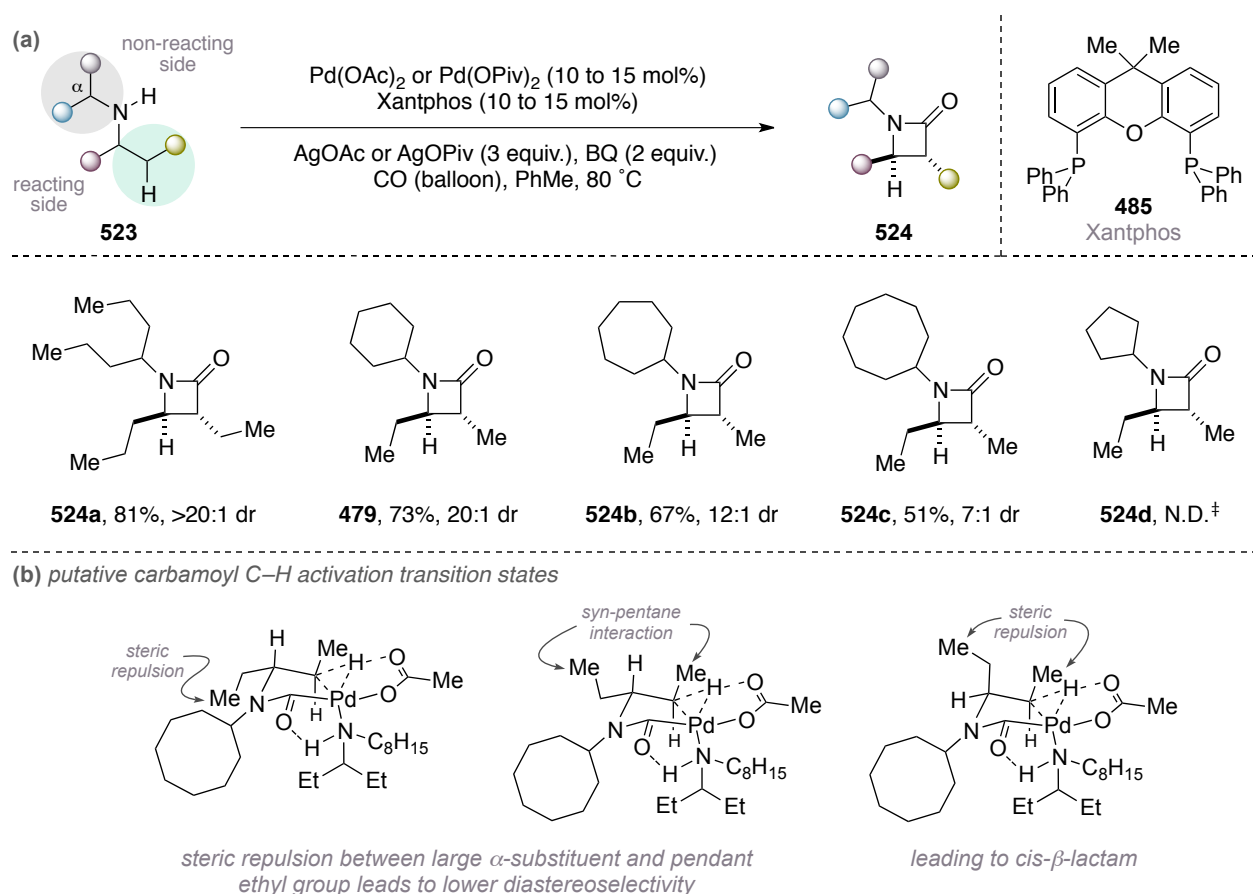
Given the critical effect of CO concentration on the outcome of the reaction, lowering the temperature to 80 °C gave an increase in the yield of  $\beta$ -lactam **493** to 82%; the solubility of CO in solution increases with decreasing temperature. Furthermore, only trace amounts of *N*-acetylated amine **522** could be observed under these conditions. Fortuitously, the reaction could be scaled up to 0.3 mmol without loss in yield; however, performing the reaction with efficient stirring 500–750 rpm using a large oval shaped stirrer bar in a 10 mL round-bottomed flask was crucial in obtaining reproducible results (Scheme 107).



**Scheme 107** | Optimized conditions for the Pd-catalyzed carbonylation of di(pentan-3-yl)amine

With optimal conditions in hand, we turned our attention to the scope of amines able to undergo  $\beta$ -C–H carbonylation (Scheme 108a). With the help of Dr J. Cabrera-Pardo and Dr M. Nappi, we first evaluated the ‘all-homologated’ di(heptan-4-yl)amine substrate **523a**. Pleasingly, despite greater steric hindrance, the  $\beta$ -lactam product **524a** was obtained in a similar 81% yield (>20:1 d.r.). Turning our attention back to *N*-(pentan-3-yl)cyclohexylamine **477**, performing the reaction at 80 °C led to an improved 73% yield and excellent diastereoselectivity **479** (20:1 d.r.). Along these lines, both the 7-

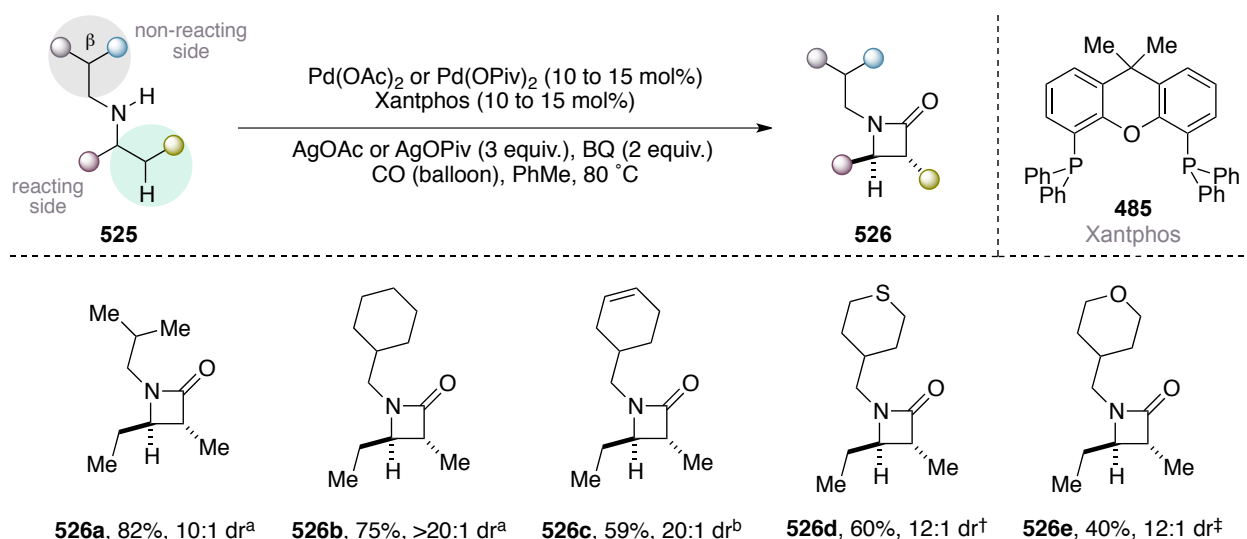
memebred **523b** and 8-membered ring **523c** analogues were tested under the reaction conditions. Pleasingly both amines were compatible, delivering the desired β-lactam products **524b** and **524c** in 67% and 51% yield respectively. Interestingly, the diastereoselectivities were found to decrease with increasing ring-size, from 20:1 (C<sub>6</sub>) to 12:1 (C<sub>7</sub>) and 7:1 (C<sub>8</sub>), possibly as a result of increasing steric interactions between the ‘inert’ cycloalkyl substituent and pendant ethyl chain in the carbamoyl C–H activation transition state (Scheme 108b). Curiously, *N*-(pentan-3-yl)cyclopentylamine **523d** afforded a complex mixture of β-lactams whereby activation appeared to occur on both the cyclic and acyclic substituents. In order to avoid potential mixture of mixtures of β-lactam products, we set about developing a class of amine substrates that would undergo regioselective β-C–H activation.



**Scheme 108** | (a) Substrate scope for α-substituted alkylamine carbonylation. (b) Putative carbamoyl transition state model leading to *cis*-β-lactam. <sup>‡</sup>Reaction conducted by Dr J. Cabrera-Pardo

Given that substituents at the α-position can have an adverse impact on the diastereoselectivity, we investigated how substitution at the corresponding β-position **525** would be tolerated (Scheme 109). Pleasingly, amines bearing β-branched substituents underwent exclusive C–H carbonylation on the opposing α-branched 3-pentyl chain; however, significant amounts of acetylated amine by-products were observed, reducing the overall efficacy of the transformation. In order to remedy this, the reactions were re-optimized using Pd(OPiv)<sub>2</sub> and AgOPiv; the more sterically encumbered Piv<sub>2</sub>O

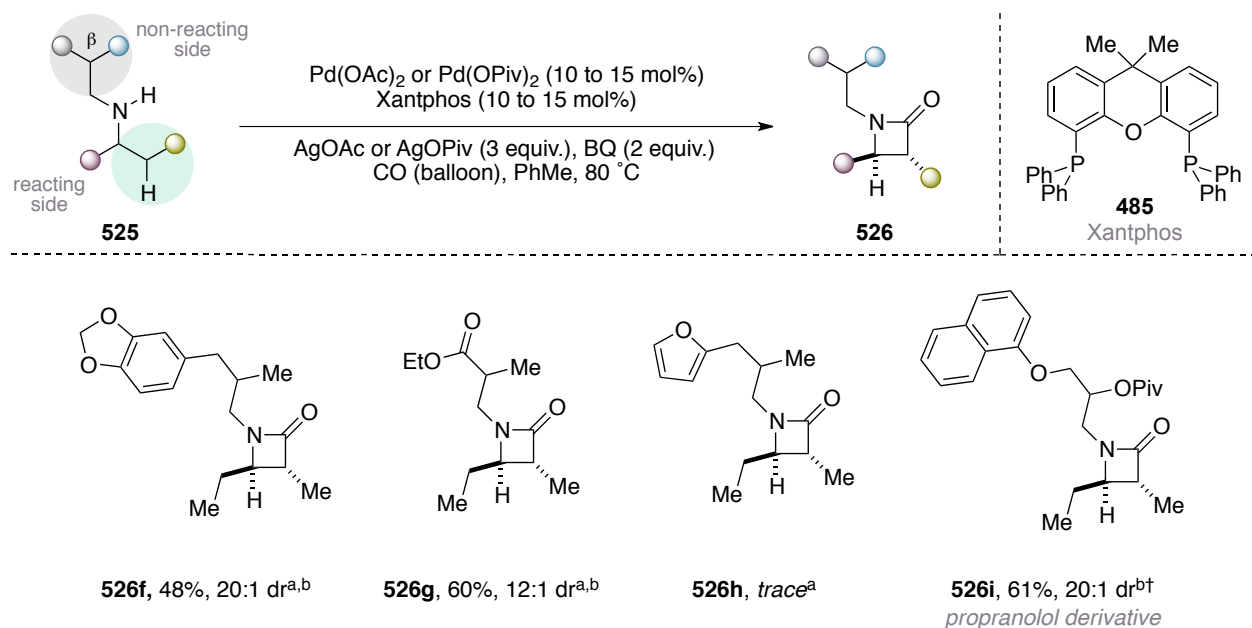
reacting slower with the less-hindered amine substrates under the reaction conditions. As a result, both isobutyl **525a** and cyclohexylmethyl **525b** amines afforded the  $\beta$ -lactam products **526a** and **526b** in 82% (10:1 d.r.) and 75% (>20:1 d.r.) yields respectively. Given the higher diastereoselectivity observed with the larger cyclohexylmethyl amine, similar ether **525e**, thioether **525d** and alkenyl **525c** substituents were tested. In line with previous observations<sup>429</sup>, both thio- and alkenyl-substituted  $\beta$ -lactams **526d** and **526c** were furnished in good yields and diastereoselectivities (60%, 12:1 d.r.; 59%, 20:1 d.r.); groups known to undergo deleterious oxidation/migration side reactions and/or poison Pd-catalysts<sup>435</sup>. The corresponding tetrahydropyran-derived amine **525e** delivered the product **526e** in a lower 40% yield. While the diastereoselectivity across the  $\beta$ -lactam core's remained high, disappointingly, there was no diastereocontrol with respect to the groups present on the non-reactive amine substituent. As a result, such amines bearing diastereotopic substituents yielded  $\beta$ -lactam products in a 1:1 mixture of diastereomers, each with the diastereoselectivity across the  $\beta$ -lactam as stated (Scheme 109).



**Scheme 109** | Substrate scope for  $\beta$ -substituted alkylamine carbonylation. <sup>a</sup>Reaction conducted using  $Pd(OPiv)_2$  (10 mol%) and AgOPiv (3 equiv.). <sup>b</sup>Product exists as 1:1 mixture of diastereomers with d.r. stated across the  $\beta$ -lactam.

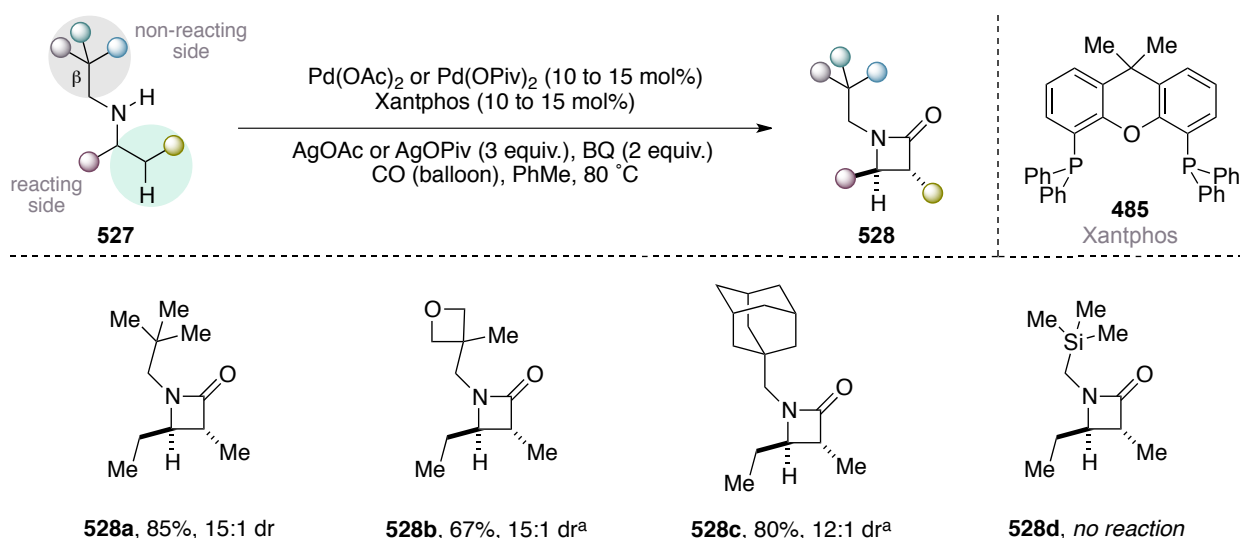
<sup>†</sup>Reaction conducted by Dr M. Nappi. <sup>‡</sup>Reaction conducted by Dr J. Cabrera-Pardo

Importantly, other  $\beta$ -functionality including an electron-rich methylenedioxybenzyl and ethyl ester substituent were well tolerated, furnishing the  $\beta$ -lactams **526f** and **526g** in 48% and 60% yield respectively (d.r. > 12:1) without any competing oxidative or retro-Aza-Michael decomposition observed (Scheme 110). Moreover, pivalate-protected propranolol analogue **525i**, an important beta-blocker drug, underwent selective C–H carbonylation to generate the  $\beta$ -lactam product **526i** in 61% yield (20:1 d.r.). Unfortunately the analogous (2-furyl)methyl branched amine **525h** underwent decomposition, affording the desired product **526h** in only trace amounts visible by <sup>1</sup>H NMR.



**Scheme 110** | Substrate scope for β-substituted alkylamine carbonylation. <sup>a</sup>Reaction conducted using Pd(OPiv)<sub>2</sub> (10 mol%) and AgOPiv (3 equiv.). <sup>b</sup>Product exists as 1:1 mixture of diastereomers with d.r. stated across the β-lactam. <sup>†</sup>Reaction conducted by Dr M. Nappi.

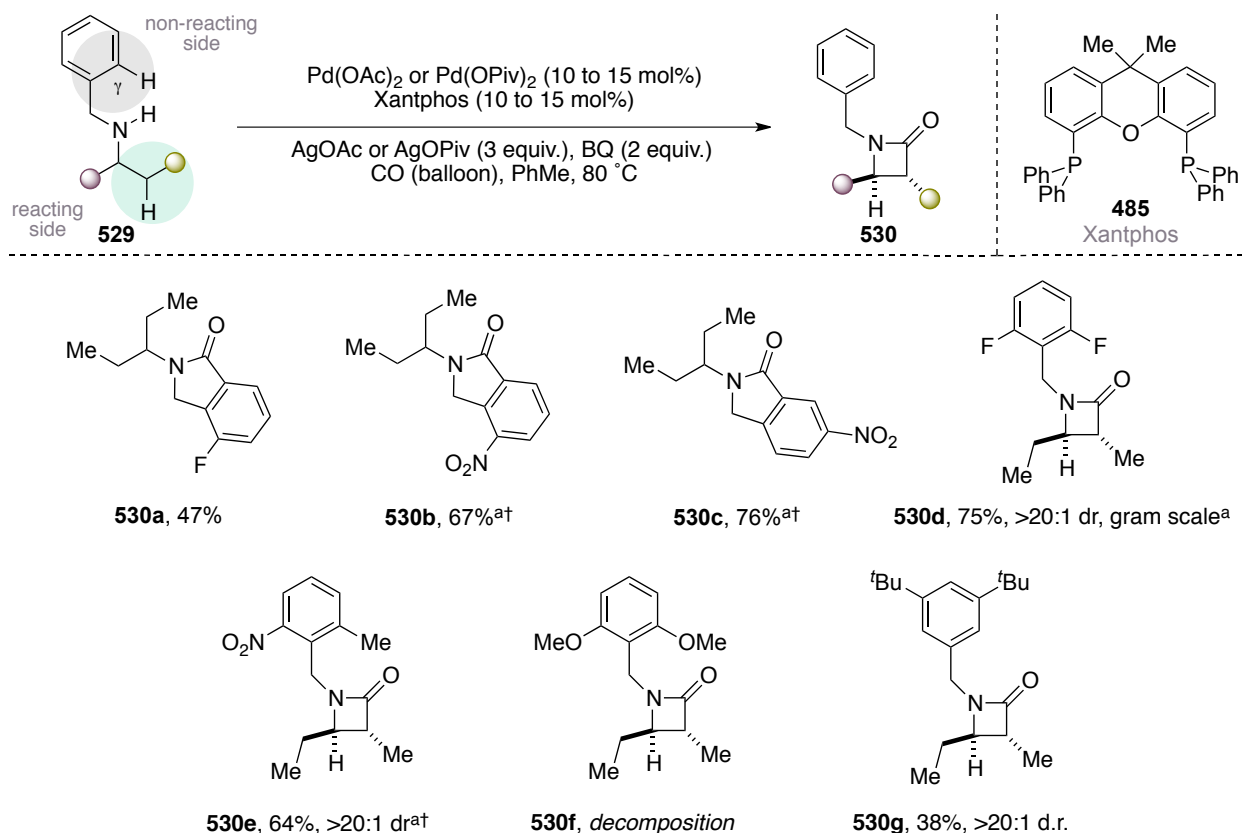
Having established that β-substituents were well tolerated in the reaction, giving rise to high levels of regiocontrol, we set about investigating the effect of β-quaternary centres **527** (Scheme 111). Remarkably, neopentyl-derived amine **527a** underwent β-C–H carbonylation **528a** in 85% yield (15:1 d.r.), an increased yield compared with the model substrate di(pentan-3-yl)amine **492** with twice the available methylene C–H bonds. In addition, (3-methyloxetan-3-yl)- **527b** and adamantylmethyl **527c** substituted amines underwent carbonylation to afford the products **528b** and **528c** in 80% and 67% yields respectively; impressively, little decomposition of the oxetane was observed under the Lewis acidic reaction conditions. Intriguingly, the silicon analogue of neopentylamine **527d** did not undergo reaction to form the desired product **528d**, returning only unreacted starting material. This lack of reactivity could be tentatively ascribed to destabilization of the anionic-like Pd–amido species via hyperconjugation<sup>480</sup>.



**Scheme 111** | Substrate scope for  $\beta$ -quaternary alkylamine carbonylation. <sup>a</sup>Reaction conducted using  $Pd(OPiv)_2$  (10 mol%) and AgOPiv (3 equiv.)

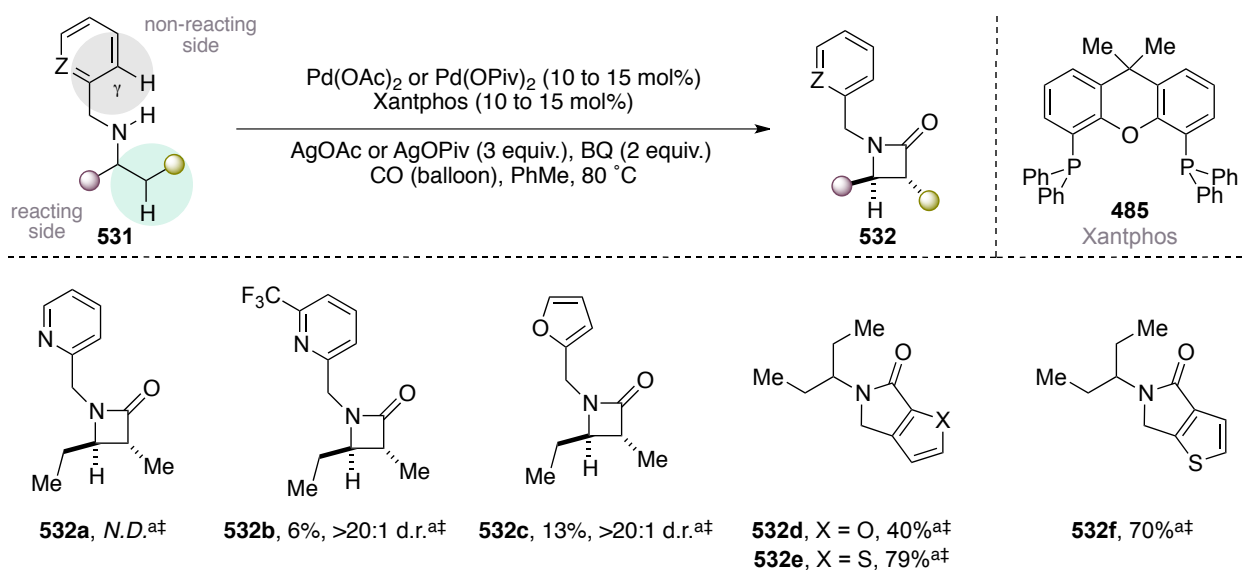
Benzylamines are a ubiquitous functional group amongst pharmaceutically relevant molecules<sup>481</sup>. Hence, their participation in a selective  $\beta$ -C( $sp^3$ )–H carbonylation methodology would greatly increase the synthetic relevance of such as transformation. However, the  $\gamma$ -C( $sp^2$ )–H activation of benzylamines has been extensively studied by Daugulis<sup>482</sup>, Shi<sup>483</sup>, Yu<sup>484,485</sup>, Garcia<sup>486</sup> and Dixon<sup>487</sup>. In particular, the Pd-catalyzed carbonylation of benzylamines to form benzolactams has been widely reported by Orito<sup>488,489</sup>, Shi<sup>490</sup>, and Garcia and Granell<sup>491,492</sup>. Given that C( $sp^2$ )–H bonds are traditionally more reactive towards C–H activation than their  $sp^3$ -hybridized counterparts<sup>298</sup>, we were unsure as to whether any regiocontrol would be exhibited under our optimized reaction conditions. A series of *o*- and *p*-substituted electron-deficient *N*-(pentan-3-yl)benzylamines **529** were subjected to the reaction conditions due to their lower reactivity towards nucleophilic palladation (Scheme 112)<sup>493</sup>. Unfortunately,  $\gamma$ -C( $sp^2$ )–H was observed in all cases, forming the benzolactam products **530a–530c** in moderate to good yields. In order to circumvent this issue, 2,6-disubstituted benzylamines were prepared and subjected to the carbonylation methodology. Pleasingly, *N*-(2,6-difluorobenzyl)pentan-3-amine **529d** underwent smooth carbonylation to form the  $\beta$ -lactam product **530d** in 75% yield (>20:1 d.r.). Conveniently, the reaction could be performed on a gram-scale without any loss in yield. Additionally, photolabile 2-methyl-6-nitrobenzylamine **529e** afforded the protected  $\beta$ -lactam **530e** in 64% yield (*vide infra*). Unfortunately, electron-rich 2,6-dimethoxybenzylamine **529f** underwent oxidative decomposition under the reaction conditions, presumably via facile  $\beta$ -hydride elimination and subsequent hydrolysis of the imine. Remarkably, 3,5-di-*tert*-butylbenzylamine **529g**, containing both *o*-hydrogens, furnished the desired  $\beta$ -lactam **530g** in 38% yield (>20:1 d.r.) without any of the corresponding benzolactam. It can be reasoned that

steric repulsion caused by the *tert*-butyl groups during the CMD transition states disfavors activation of the  $\gamma$ -C( $sp^2$ )–H bonds.



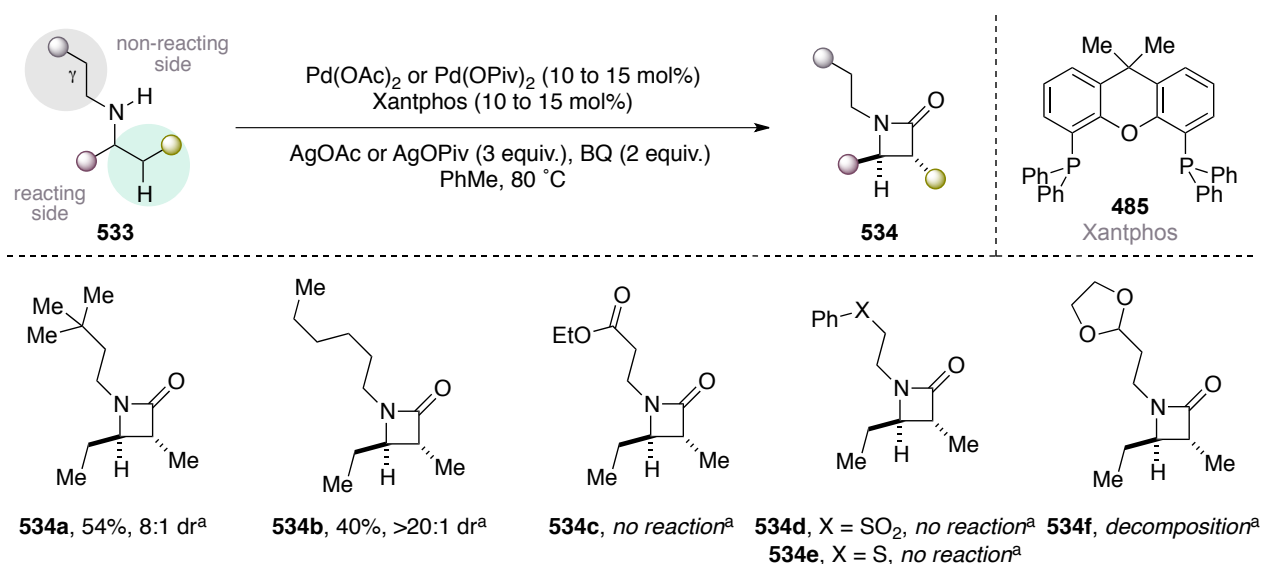
**Scheme 112** | Substrate scope for benzylamine carbonylation. <sup>a</sup>Reaction conducted using  $Pd(OPiv)_2$  (10 mol%) and AgOPiv (3 equiv.). <sup>†</sup>Reaction conducted by Dr M. Nappi

At the same time, Dr J. Cabrera-Pardo investigated the corresponding heterobenzylamines under the reaction conditions (Scheme 113). While (2-pyridyl)methylamine **531a** returned only starting material, doubtless due to the formation of a stable *bis*-chelate, (6-(trifluoromethyl)-2-pyridyl)methylamine **531b** generated 6% of the  $\beta$ -lactam product **532b** (>20:1 d.r.). A slightly improved yield was observed using (2-furyl)methylamine **531c**, resulting in 13% of the  $\beta$ -lactam product **532c**, however significant amounts of decomposition were observed. The corresponding (3-furyl)methylamine **531d** resulted in formation of the heterobenzolactams **532d** in 40% yield, with C–H activation occurring exclusively at the 2-position of the furan. Regrettably, both 2- and (3-thiophenyl)methylamines **531e** and **531f** underwent  $\gamma$ -C( $sp^2$ )–H activation, affording the heterobenzolactams **532e** and **532f** in 70% and 79% yield respectively.



**Scheme 113** | Substrate scope heterobenzyamine carbonylation. <sup>a</sup>Reaction conducted using  $Pd(OPiv)_2$  (10 mol%) and AgOPiv (3 equiv.). <sup>†</sup>Reaction conducted by Dr J. Cabrera-Pardo

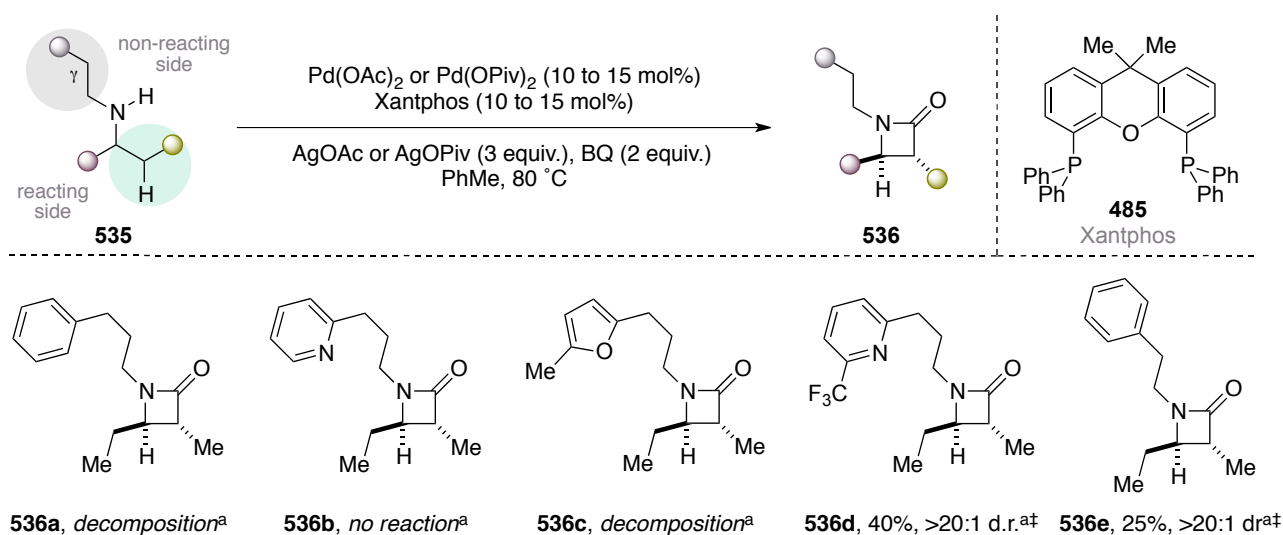
Ascertaining that both  $\alpha$ - and  $\beta$ -substituted 3-pentylamines were competent substrates for  $\beta$ -C( $sp^3$ )–H carbonylation, we turned our focus towards less-hindered amines **533** (Scheme 114). While neopentylamine served as the highest yielding substrate, the homologated 3,3-dimethylbutylamine **533a** underwent carbonylation to generate the  $\beta$ -lactam product **534a** in a lower 54% yield (8:1 d.r.). Moreover, *n*-hexylamine substrate **533b** afforded the desired product **534b** in 40% yield, albeit with greater diastereoselectivity (>20:1 d.r.). In order to explore the scope of simple linear alkylamines, a series of  $\beta$ -substituted substrates were prepared and subjected to the carbonylation conditions.  $\beta$ -amino ester **533c** and sulfone **533d**, prepared via an Aza-Michael addition, did not furnish any of the desired  $\beta$ -lactam products **534c** and **534d**, returning only unreacted starting material. Similarly, the corresponding sulfide **533e** and (1,3-dioxolan-2-yl)ethylamine **533f** substrate did not afford any of the desired products **534e** and **534f**.



**Scheme 114** | Substrate scope less-hindered amine carbonylation. <sup>a</sup>Reaction conducted using  $\text{Pd}(\text{OPiv})_2$  (10 mol%) and  $\text{AgOPiv}$  (3 equiv.).

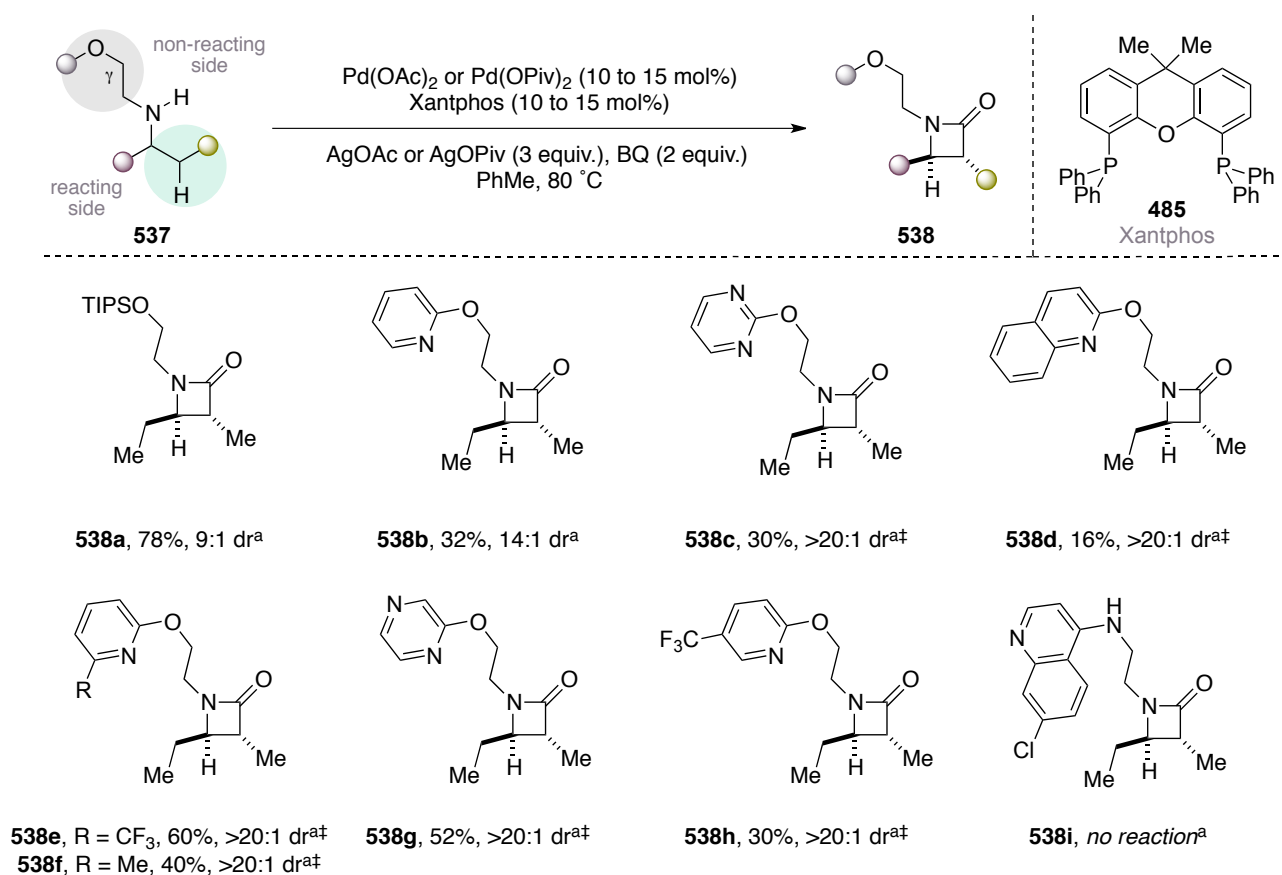
Although significant  $\text{C}(\text{sp}^2)\text{--H}$  activation was observed with benzylamine-derived substrates, we were curious to establish whether phenethyl- and phenpropylamines **535** would be tolerated given the formation of kinetically unfavourable 7- and 8-membered ring palladacycles (Scheme 115)<sup>494</sup>. Disappointingly, phenpropylamine-derived amine **535a** underwent significant decomposition under the reaction conditions, affording only trace product **536a** by <sup>1</sup>H NMR. In the same vein, (2-pyridyl)- and (2-furyl)propylamine-derived amines **535b** and **535c** did not give rise to any β-lactam products **536b** and **536c**. Due to the possible formation of a stable unreactive chelate, (6-(trifluoromethyl)-2-pyridyl)propylamine **535d** was synthesized and tested under the reaction conditions; the α-CF<sub>3</sub> substituent increasing the sterics as well as effectively dampening the pyridyl σ-donating ability<sup>495</sup>. Opportunely, the desired β-lactam product **536d** was generated in a 40% yield (>20:1 d.r.). Interestingly, phenethylamine **535e** proved a more fruitful substrate, delivering the β-lactam product **536e** in 25% yield, crucially without competing  $\text{C}(\text{sp}^2)\text{--H}$  activation.





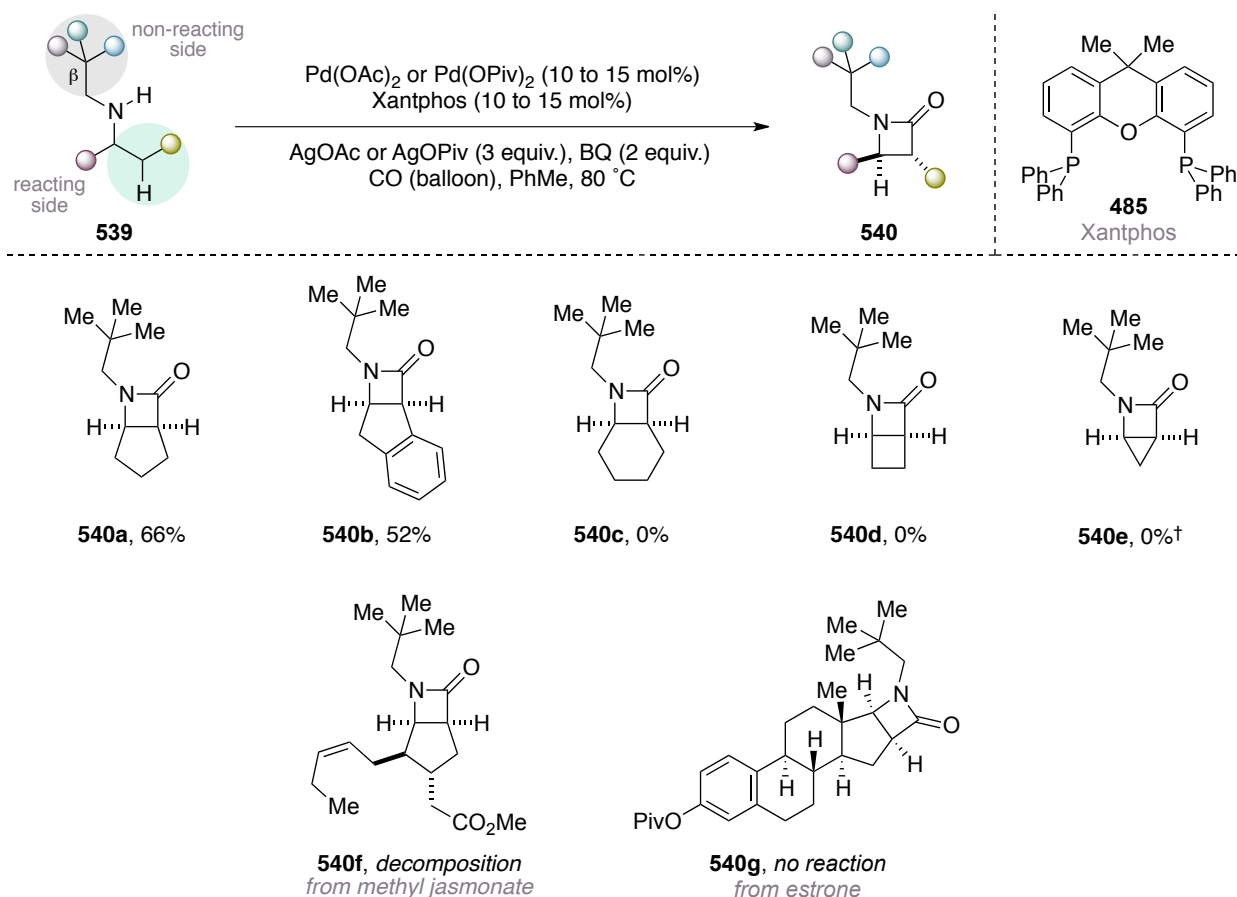
**Scheme 115** | Substrate scope less-hindered amine carbonylation. <sup>a</sup>Reaction conducted using  $Pd(OPiv)_2$  (10 mol%) and AgOPiv (3 equiv.). <sup>†</sup>Reaction conducted by Dr J. Cabrera-Pardo

Gratifyingly, synthetically versatile  $\beta$ -aminoalcohol-derived substrates **537** proved more productive under the carbonylation methodology (Scheme 116). TIPS-protected ethanolamine-derived substrate **537a** underwent C–H carbonylation to deliver the  $\beta$ -lactam product **538a** in an impressive 78% (9:1 d.r.), notably, no C–H activation was observed at the  $\alpha$ -ethereal protons despite the potential for an  $\alpha$ -heteroatom effect<sup>496</sup>. As a result of the high yield obtained with the  $\beta$ -aminoalcohol scaffold, we were keen to encompass more functionality within this framework. Where before (2-pyridyl)propylamine **535b** did not give rise to any of the desired product, the related (2-pyridinyloxy)ethylamine **537b** furnished the  $\beta$ -lactam **538b** in a 32% yield (14:1 d.r.). Other heteroaryl substituted  $\beta$ -aminoalcohol substrates were readily prepared via  $S_NAr$  of the halo-substituted heteroaromatic. Pleasingly, (2-pyrimidinyloxy)ethylamine and (2-quinoloyloxy)-substrates **537c** and **537d** proved competent under the reaction conditions, furnishing the desired  $\beta$ -lactams **538c** and **538d** in 30% and 16% yields respectively. In accordance with previous findings, (6-(trifluoromethyl)-2-pyridyloxy)ethylamine **537e** generated the  $\beta$ -lactam product **538e** in an improved 60% yield (>20:1 d.r.) compared with the parent heterocycle. It should be noted that both (6-(methyl)-2-pyridyloxy)ethylamine and (5-(trifluoromethyl)-2-pyridyloxy)ethylamine substrates **537f** and **537h** delivered the  $\beta$ -lactam products **538f** and **538h** in 40% and 30% respectively, highlighting the unique stereoelectronic effect imparted by the 6-(trifluoromethyl) substituted pyridine. Interestingly, (2-pyrazinyloxy)ethylamine **537g** afforded the  $\beta$ -lactam product **538g** in a 52% yield (>20:1 d.r.), in keeping with the reduced basicity of the  $N(sp^2)$  lone pair<sup>497</sup>. Unfortunately, chloroquinoline-derived ethylene diamine substrate **537i**, an important motif present in antimalarial pharmaceuticals<sup>498</sup>, failed to deliver any of the desired  $\beta$ -lactam product **538i**.



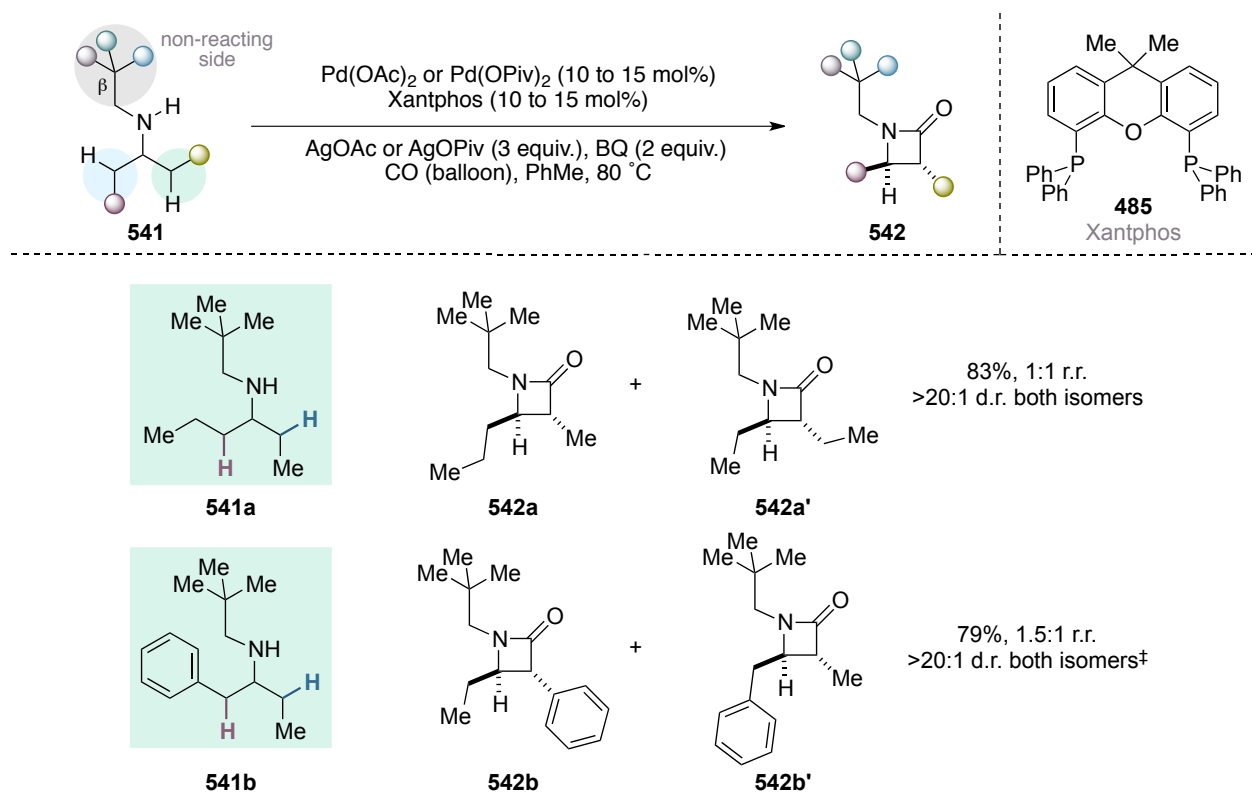
**Scheme 116** | Substrate scope for β-aminoalcohol carbonylation. <sup>a</sup>Reaction conducted using  $\text{Pd}(\text{OPiv})_2$  (10 mol%) and AgOPiv (3 equiv.). <sup>†</sup>Reaction conducted by Dr J. Cabrera-Pardo

Having previously observed that *N*-(pentan-3-yl)cyclopentylamine **523d** afforded a mixture of β-lactam products, we reasoned that *N*-(neopentyl)cyclopentylamine **539a** should undergo exclusive activation on the cyclic methylene C–H bonds (Scheme 117). Pleasingly, when subjected to the reaction conditions, the amine furnished the *cis*-fused β-lactam product **540a** in 66% yield. Moreover, *N*-(neopentyl)-2-indanamine **539b** served as a competent substrate, forming tricyclic *cis*-fused β-lactam **540b** in 52% yield. The analogous cyclohexyl, cyclobutyl and cyclopropyl amine substrates **539c–539e** did not afford any of the desired β-lactam products **540c–540e**. Unfortunately, neither more complex estrone nor methyl jasmonate-derived amines **539f** and **539g** delivered the desired fused β-lactam products **540f** and **540g**, presumably due to increased sterics around the cyclopentane ring.



**Scheme 117** | Substrate scope for cycloalkylamine carbonylation. †Reaction conducted by Dr M. Nappi

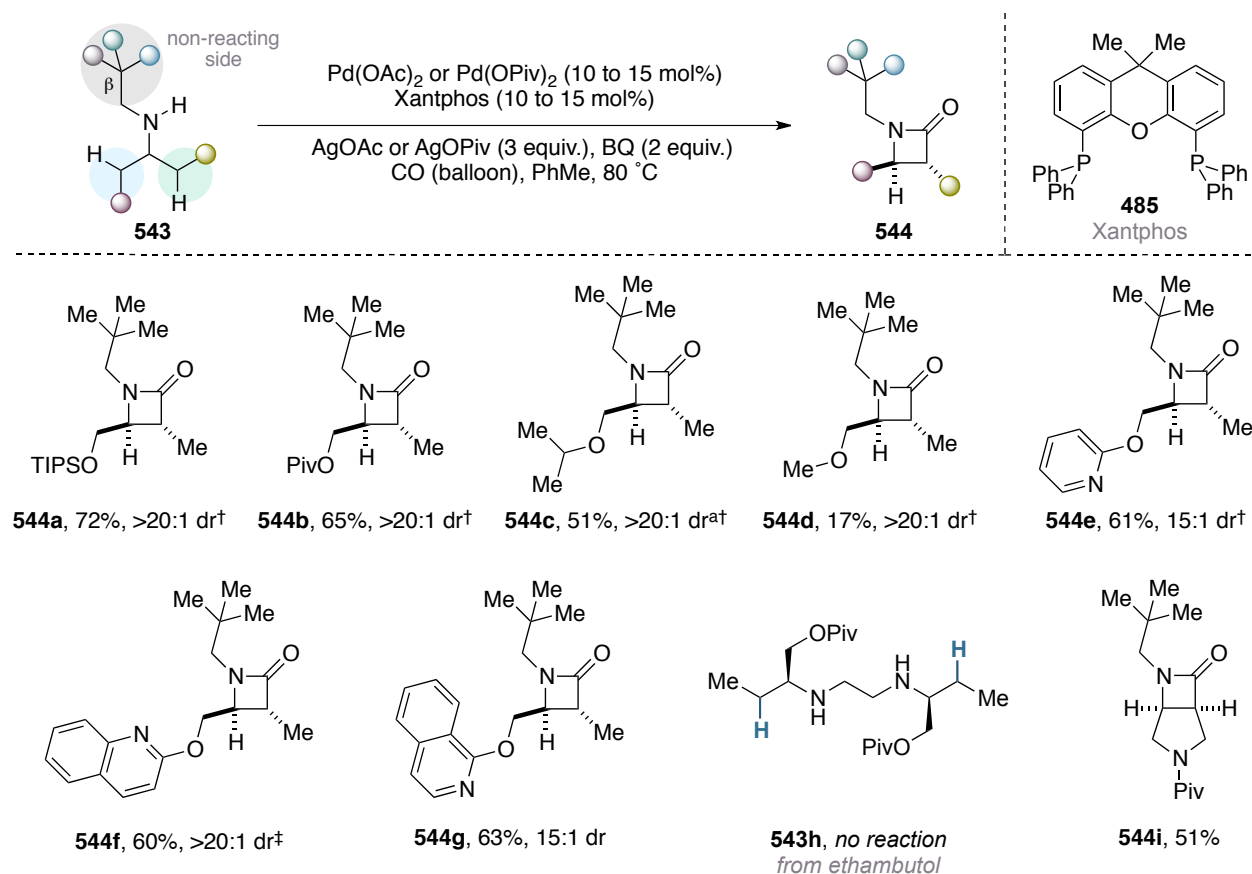
We next turned our attention to examining the selectivity of the  $\beta$ -carbonylation process between different methylene C–H bonds – a notoriously challenging undertaking due to the near identical steric and thermodynamic properties<sup>499</sup>. In order to explore this more closely, we first decided to investigate the selectivity between two different methylene C–H bond environments in a 3-pentyl chain<sup>261</sup>; therefore, we required the other amine group to be inert towards C–H activation. Naturally, the neopentyl group served as the obvious choice given the high yield obtained using *N*-(pentan-3-yl)neopentylamine **527a** as a substrate. We first evaluated whether any selectivity would be imparted in the case of *N*-(hexan-3-yl)neopentylamine **541a** (Scheme 118). Unsurprisingly, the steric and electronic similarity between the ethyl and propyl chains led to no regiocontrol, delivering the  $\beta$ -lactams **542a/542a'** a 1:1 mixture of diastereomers in 83% yield (>20:1 d.r.). Dr J. Cabrera-Pardo next examined whether any useful selectivity could be generated between ethyl and benzyl substituents **541b** (Scheme 118). Although the  $\beta$ -lactam products **542b/542b'** were afforded in good yields (79% combined), little selectivity was observed between the two methylene C–H bonds (1.5:1 r.r.), perhaps indicating that the reaction is under thermodynamic and not kinetic control and that C–H activation is reversible<sup>429</sup>.



**Scheme 118** | Substrate scope for selective methylene alkylamine carbonylation. <sup>‡</sup>Reaction conducted by Dr J. Cabrera-Pardo

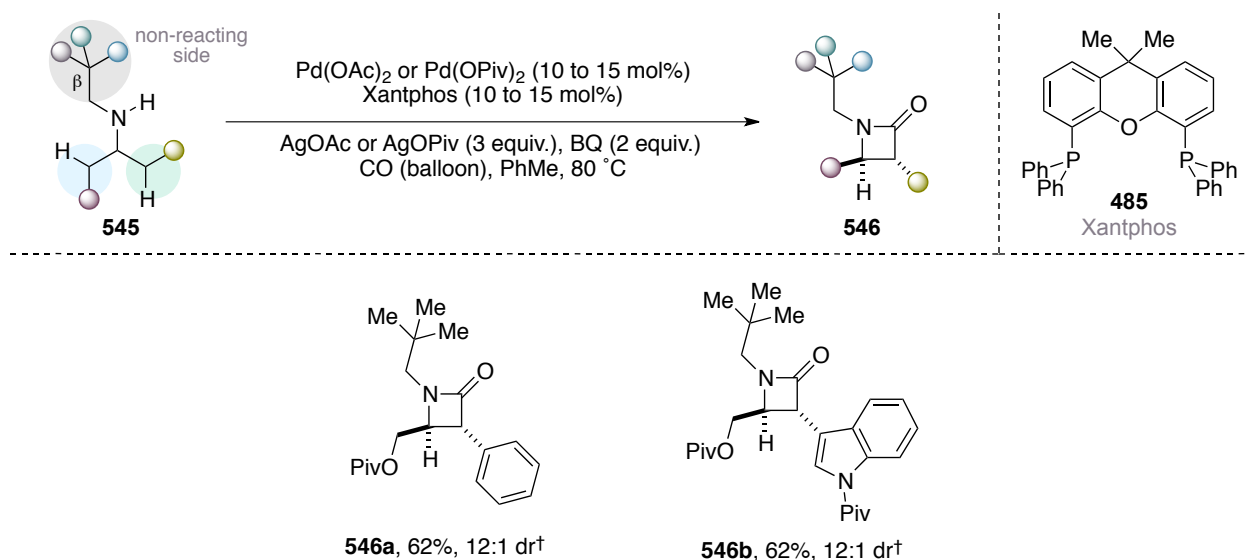
Inspired by our previous observation that β-aminoalcohols underwent C–H activation in good yields without any competing activation adjacent to the oxygen, Dr M. Nappi synthesized TIPS-protected 2-(neopentylamine)butan-1-ol **543a**. Delightfully, when subjected to the reaction conditions, the β-lactam product **544a** was formed in a 72% yield (>20:1 d.r.); no C–H activation was observed at the β-position containing the oxygen substituent (Scheme 119). Additionally, both pivalate ester and isopropyl ether substituents **543b** and **543c** were well tolerated, with regioselective C–H activation delivering the β-lactam products **544b** and **544c** in 65% and 51% yields respectively (>20:1 d.r.). The corresponding methyl ether **543d** underwent significant decomposition, delivering the β-lactam **544d** in a 17% yield. Furthermore, heteroaryloxy substituents were similarly well tolerated under the reaction conditions, without the necessity for deactivating trifluoromethyl substituents. Simple unsubstituted (2-pyridyloxy) substituted amine **543e** furnished the desired β-lactam **544e** in 61% yield (15:1 d.r.) with exclusive activation occurring at the distal methylene C–H bond. Comparably, (2-quinoloyloxy) and (1-isoquinoloyloxy)-derived substrates **543f** and **543g** furnished the corresponding products **544f** and **544g** in 60% and 63% yields respectively. Regrettably, pivalate protected-ethambutol **543h**, a diamine used in the treatment of tuberculosis<sup>500</sup>, failed to deliver any of the desired β-lactam or di-β-lactam product resulting from dual C–H activation – presumably due to the formation of the stable bis-chelate. In line with the methylene C–H activation of *N*-

(neopentyl)cyclopentylamine-derived amine **539a**, we were keen to establish whether the selectivity observed in acyclic systems would translate to saturated heterocycles. We synthesized pivalate-protected 3-(neopentylamine)pyrrolidine **543i** in three steps from the Cbz-protected 3-pyrrolidone. When subjected to the reaction conditions, a single *cis*-fused  $\beta$ -lactam product **544i** was obtained in 51% yield, wherein, C–H activation had occurred exclusively at the 4-position of pyrrolidine – distal to the heteroatom.



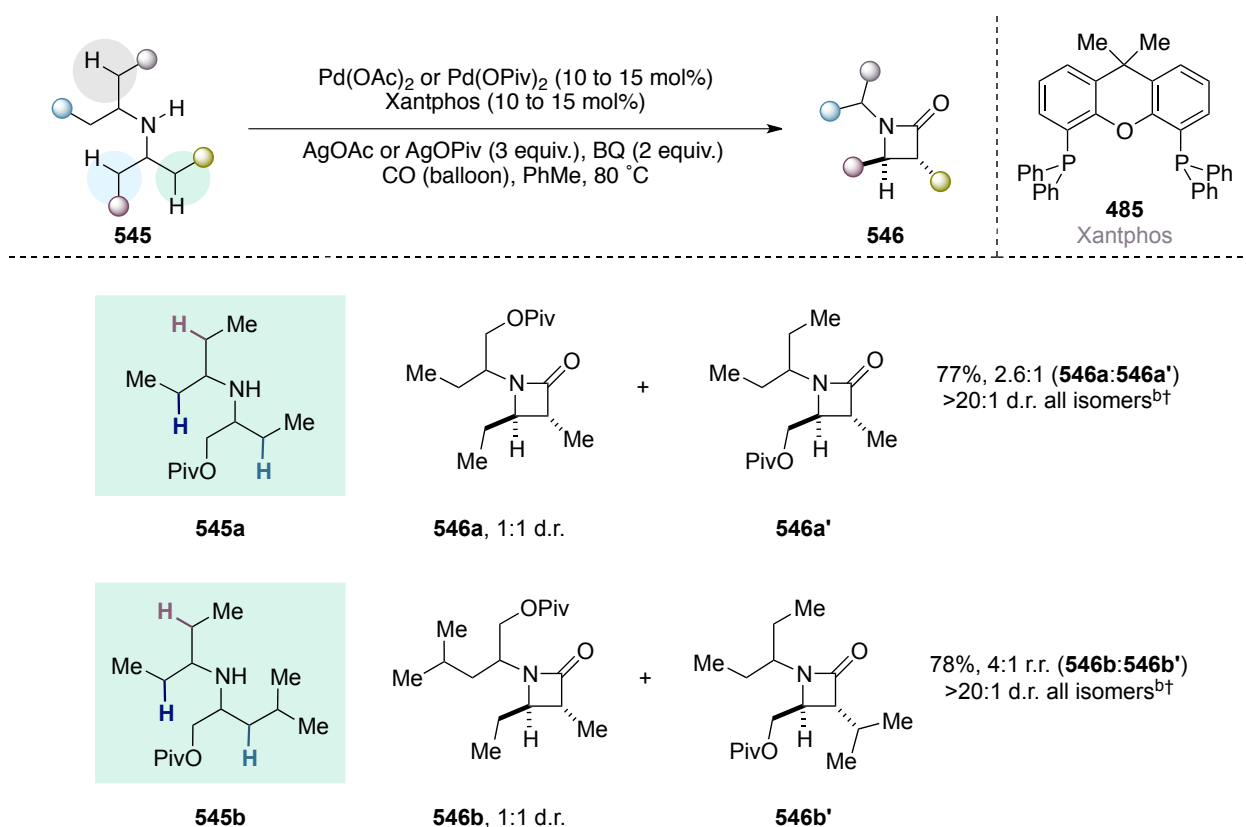
**Scheme 119** | Substrate scope for selective methylene alkylamine carbonylation. <sup>a</sup>Reaction conducted using  $Pd(OPiv)_2$  (10 mol%) and AgOPiv (3 equiv.). <sup>†</sup>Reaction conducted by Dr M. Nappi. <sup>‡</sup>Reaction conducted by Dr J. Cabrera-Pardo

Having established a blueprint for the regioselective C–H carbonylation of 3-pentylamines bearing one substituted  $\alpha$ -branch, we next turned our attention to substrates containing multiple substituents (Scheme 120). Excitingly, pivalate-protected phenylalaninol-derived amine **545a**, containing both benzylic and ethereal methylene C–H bonds, delivered a single  $\beta$ -lactam product **546a** in 62% (12:1 d.r.) whereby C–H activation had occurred exclusively at the benzylic position. Along these lines, pivalate-protected tryptophanol **545b** underwent regioselective heterobenzylic C–H activation, furnishing the desired product **546b** in 62% yield (12:1 d.r.). Markedly, no  $C(sp^2)$ –H activation was observed, thereby conveying useful selectivity in more complex amine systems.



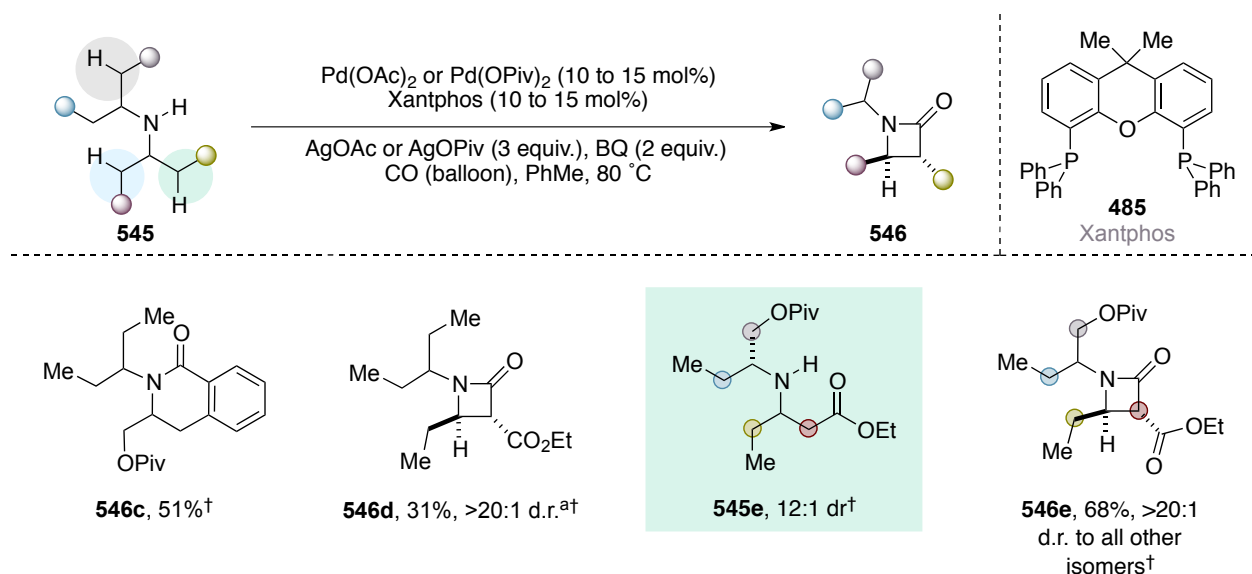
**Scheme 120** | Substrate scope for selective methylene alkylamine carbonylation. <sup>†</sup>Reaction conducted by Dr M. Nappi

In addition to testing the selectivity between two β-methylene C–H bonds, we were keen to ascertain whether any regiocontrol could be imparted with more methylene C–H bond environments (Scheme 121). In order to test this, Dr M. Nappi prepared a modified di(pentan-3-yl)amine containing a pivalate-protected alcohol **545a**. When subjected to the carbonylation conditions, a mixture of three β-lactam products was observed in 77% yield; importantly, no activation had occurred on the *O*-containing substituent. Interestingly, the product distribution showed a 2.6:1 preference for activation of the four methylene C–H bonds on the opposing amine substituent **546a** to that containing the protected alcohol **546a'** – a greater than statistical outcome. Comparably, protected *N*-(pentan-3-yl)-derived leucinol **545b** afforded a 4:1 mixture of regioisomers in 78% yield, with C–H activation occurring preferentially on the 3-pentyl chain **546b** compared to the more hindered methylene C–H bonds adjacent to the isopropyl group **546b'**.



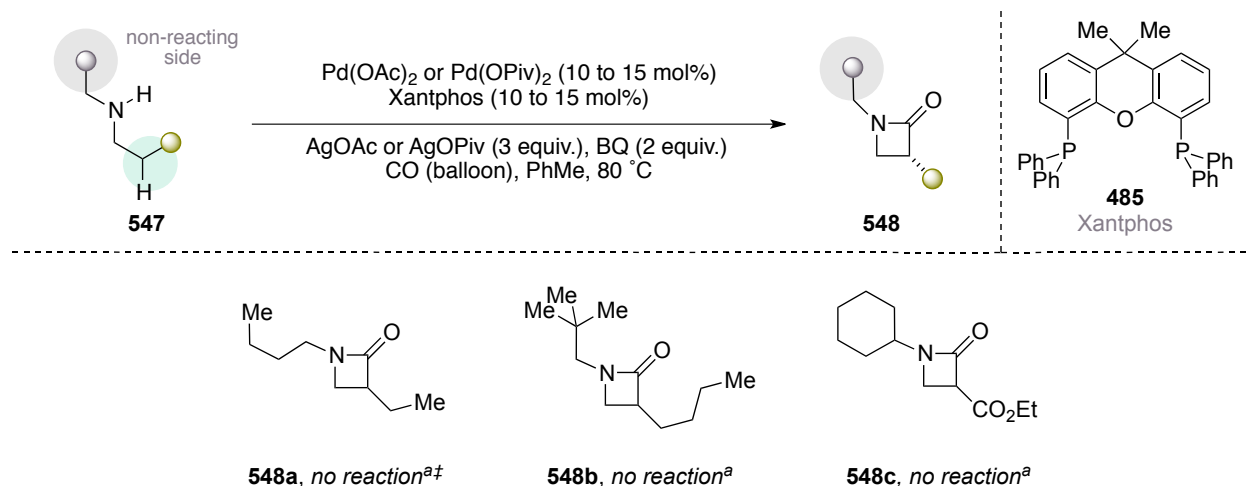
**Scheme 121** | Substrate scope for alkylamine carbonylation bearing multiple methylene C–H bonds. <sup>b</sup>Product exists as 1:1 mixture of diastereomers with d.r. stated across the  $\beta$ -lactam. <sup>t</sup>Reaction conducted by Dr M. Nappi

Contrary to earlier observations, protected *N*-(pentan-3-yl)-derived phenylalaninol **545c**, prepared by Dr M. Nappi, underwent exclusive C( $sp^2$ )–H activation to deliver the  $\delta$ -benzolactam **546c** in 51% yield (Scheme 122). However, *N*-(pentan-3-yl)-derived ethyl 3-aminopentanoate **545d** underwent  $\beta$ -C–H activation adjacent to the ester in 36% yield, critically, the only  $\beta$ -lactam **546d** product obtained (Scheme 122). Based on these collective observations, we reasoned that an amine based on the di(pentan-3-yl)amine scaffold where one amine substituent contains an ester and the other a protected alcohol, a single  $\beta$ -lactam product may be obtained from four separate C–H bond environments **545e**. Delightfully, upon subjection to the reaction conditions by Dr M. Nappi, a single  $\beta$ -lactam product **546e** was obtained in 68% yield (>20:1 d.r. to all other isomers), wherein C–H activation occurred exclusively at the position adjacent to the ester, possibly reflecting the acidity of the C–H bond or the importance of a Pd-enolate.



**Scheme 122** | Substrate scope for alkylamine carbonylation bearing multiple methylene C–H bonds. <sup>a</sup>Reaction conducted using Pd(OPiv)<sub>2</sub> (10 mol%) and AgOPiv (3 equiv.). <sup>†</sup>Reaction conducted by Dr M. Nappi

Finally, we turned our attention to the methylene C–H activation of linear alkylamines **547** (Scheme 123). Regrettably, no reaction was observed in the case of di-*n*-butylamine **547a**, *N*-(neopentyl)hexylamine **547b** or ethyl 3-(cyclohexylamine)propionate **548c** – highlighting the inherent importance of the α-branch in steering the methylene C–H bond close to the reactive Pd-centre.

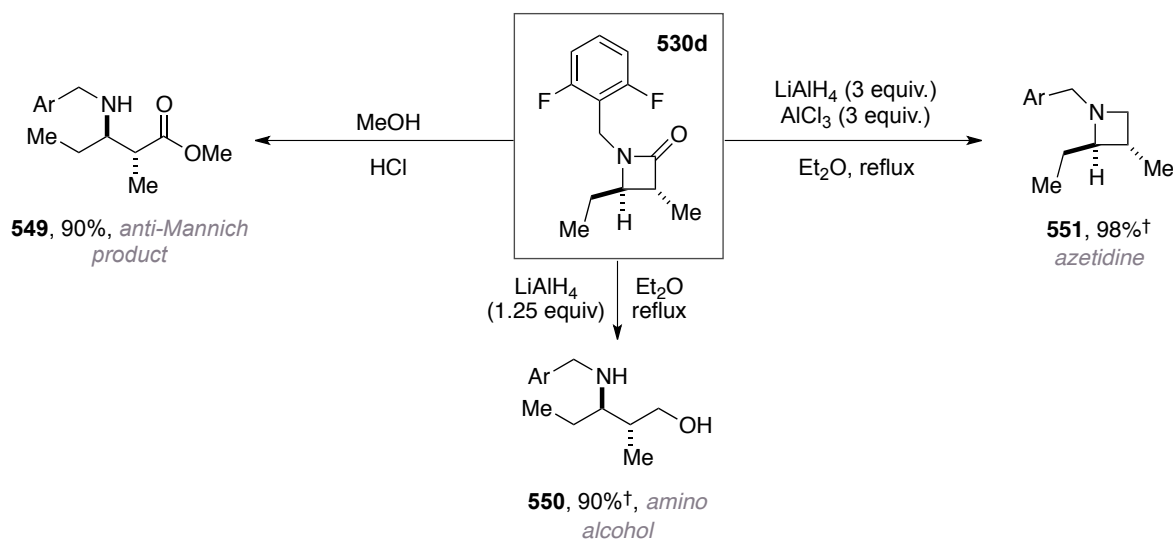


**Scheme 123** | Substrate scope for linear dialkylamine carbonylation. <sup>a</sup>Reaction conducted using Pd(OPiv)<sub>2</sub> (10 mol%) and AgOPiv (3 equiv.). <sup>†</sup>Reaction conducted by Dr J. Cabrera-Pardo

β-lactams are highly versatile heterocycles, capable of undergoing numerous transformations to generate useful building blocks<sup>501</sup>. Accordingly, acidic methanolysis delivered the corresponding β-amino ester **549** in 90% yield (Scheme 124). Importantly, the stereochemistry was consistent with that of the formal *anti*-Mannich adduct – a particularly challenging product to generate by conventional methods<sup>32</sup>. Furthermore, by careful control of the reaction conditions, reduction using

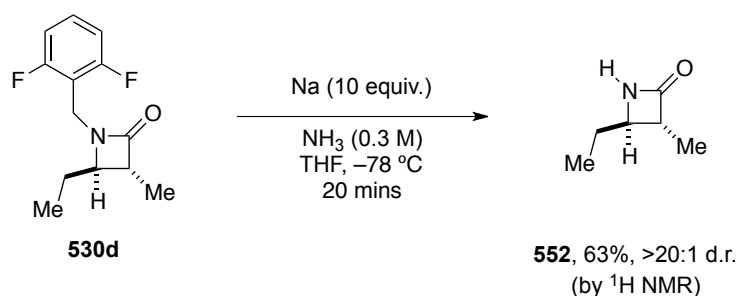


$LiAlH_4$  can deliver either the amino alcohol **550** or azetidine **551** products in high yields (90% and 98% respectively) (Scheme 124).



**Scheme 124** | Derivatization of  $\beta$ -lactam products. <sup>†</sup>Reaction conducted by Dr M. Nappi

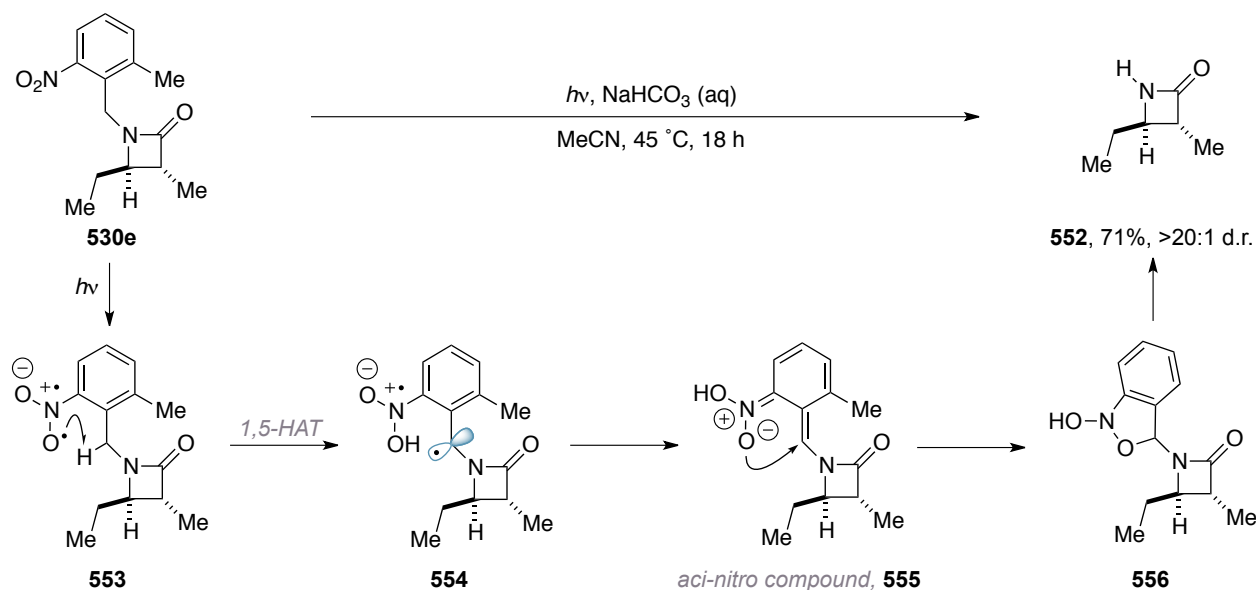
Finally, we envisaged that the development of a protocol to access the free (*NH*)-lactam would facilitate further synthetic transformations. Williams reported that *N*-benzyl substituted  $\beta$ -lactams can be cleaved in good yields using  $Na/NH_3$ <sup>502</sup>; however, given the requirement for two *ortho*-substituents we turned our attention to the 2,6-difluorobenzyl group **530d**. Although, to the best of our knowledge, the 2,6-difluorobenzyl group itself has not been used as a protecting group for amides, Borschberg and Burkard have developed a protocol for its cleavage from ethers using  $Ca/NH_3$ <sup>503</sup>. Despite early success using  $Na/NH_3$  in THF, delivering the unprotected  $\beta$ -lactam **552** in 63% yield (by  $^1H$  NMR), the reaction proved highly capricious and irreproducible (Scheme 122).



**Scheme 125** | Reductive cleavage of 2,6-difluorobenzyl protected  $\beta$ -lactam

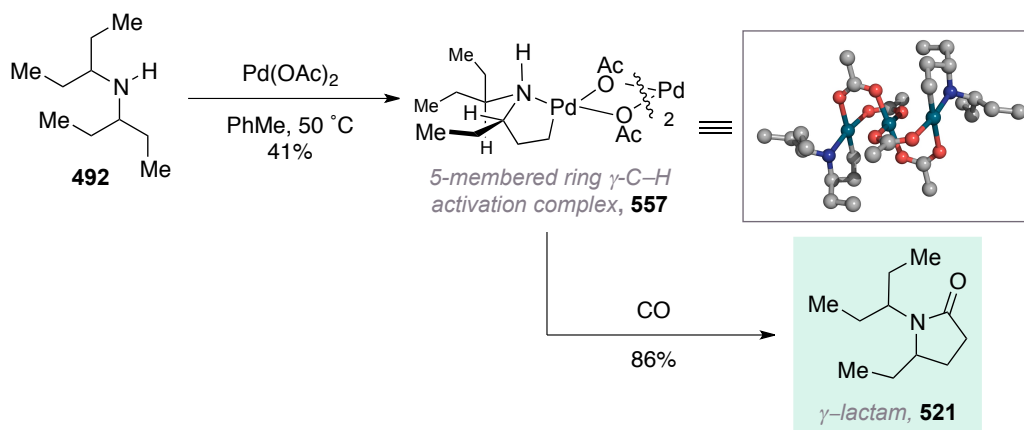
Based on the work by Williams<sup>504</sup>, Snider<sup>505</sup>, and Stoltz<sup>506</sup>, employing the 2-nitrobenzyl group as a photolabile protecting group for amides, Dr M. Nappi subsequently discovered that 2-methyl-6-nitrobenzyl  $\beta$ -lactam **530e** could undergo photochemical deprotection using UV light in 71% yield (Scheme 126). The key to the success of the reaction is a Norrish type II process wherein excitation of the nitro group **552** leads to facile 1,5-HAT from the benzylic carbon to oxygen of the nitro group **553**; driven by the greater strength of the O–H bond compared to the C–H bond. Subsequent

tautomerization to the *aci*-nitro compound **555** and intramolecular cyclization ultimately results in the formation of the nitroso hemiaminal **556**, which decomposes under the reaction conditions liberating the product **552**.



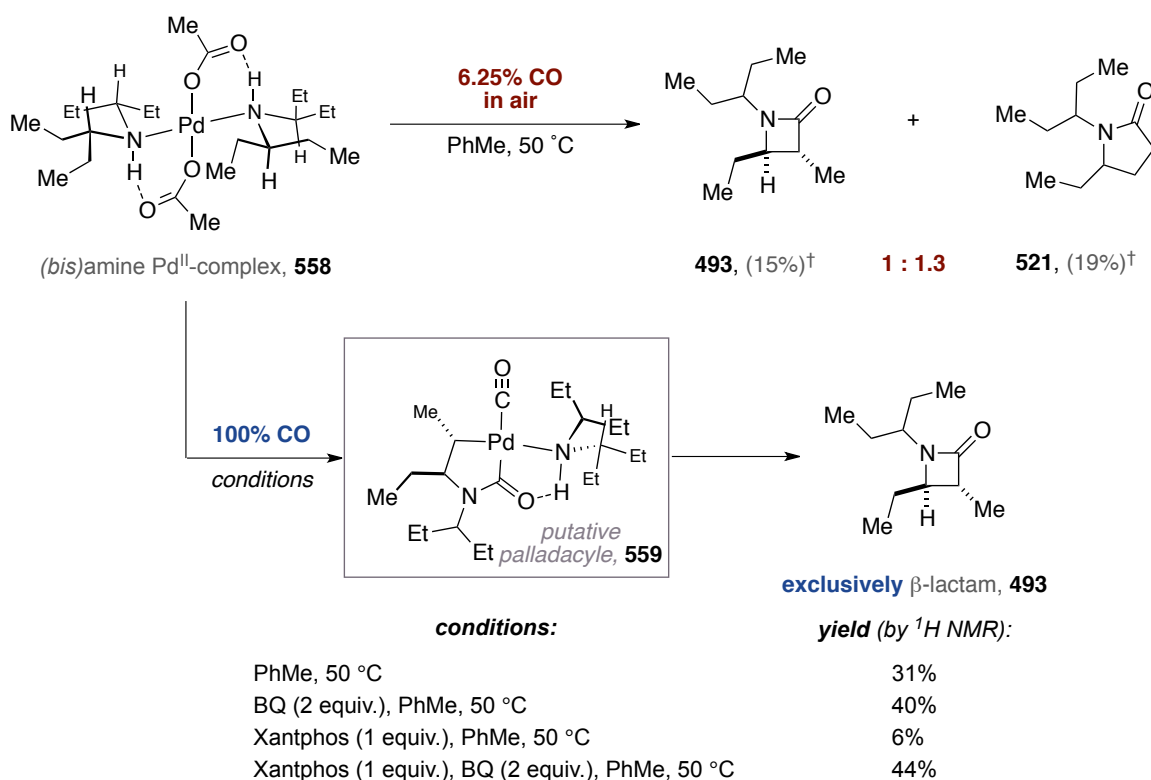
**Scheme 126** | Photochemical cleavage of nitrobenzyl β-lactam. Reaction conducted by Dr M. Nappi

Appertaining to these results, preliminary mechanistic investigations were undertaken by Dr M. Nappi in order to gain further insights into the mechanism of β-methylene C–H carbonylation. First, we wanted to benchmark the C–H activation step by treating di(pentan-3-yl)amine **492** with stoichiometric Pd(OAc)<sub>2</sub> in toluene at 50 °C (Scheme 127). Under these conditions, γ-C(*sp*<sup>3</sup>)–H activation of the terminal methyl groups occurred, delivering the 5-membered cyclopalladation complex **557** in 41% yield. Treatment of the complex with CO led to the formation of the γ-lactam **521** in 86% yield via CO insertion and reductive elimination. Given the facile γ-C(*sp*<sup>3</sup>)–H activation of the amine under these conditions, combined with the absence of the γ-lactam product under catalytic conditions, we concluded that a different reactive intermediate species must be formed.



**Scheme 127** | Cyclopalladation of di(pentan-3-yl)amine and subsequent carbonylation. Reaction conducted by Dr M. Nappi

In order to test this hypothesis, we treated the (*bis*)amine  $Pd^{II}$ -complex **558** – an established precursor for C–H activation<sup>337</sup>, under 6.25% CO/air in toluene at 50 °C (Scheme 128). Intriguingly, we found that the reaction afforded a 1.3:1 mixture of  $\gamma$ -lactam **521** to  $\beta$ -lactam **493** in 34% yield; the latter product arising from activation of the desired  $\beta$ -methylene C–H bonds. When the same (*bis*)amine  $Pd^{II}$ -complex **558** was treated under pure CO in toluene at 50 °C, the  $\beta$ -lactam **493** was formed as the exclusive in 31% yield (Scheme 128).

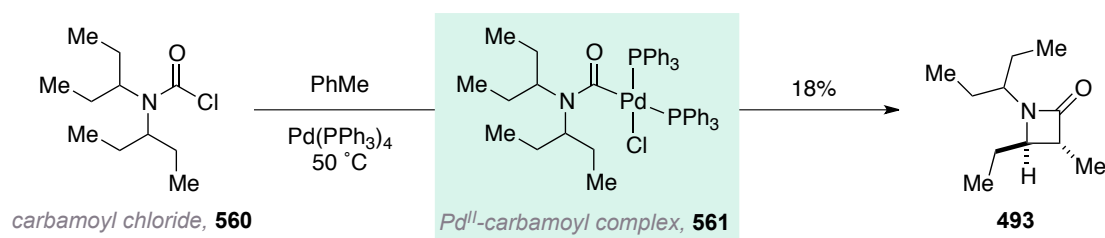


**Scheme 128** | Carbonylation studies of (*bis*)amine  $Pd^{II}$ -complex. <sup>†</sup>Reaction conducted by Dr M. Nappi

A significant increase in yield of the  $\beta$ -lactam **493** (40%) was observed when BQ (2 equiv.) was added to the reaction mixture, by contrast however, the addition of Xantphos resulted in a substantial decrease – the product **493** being generated in a mere 6% yield (Scheme 128). As a result, we believe that BQ serves to effectively promote reductive elimination of the product **493** and/or suppress side reactions, whereas Xantphos is most likely not involved in the product-forming step. A combination of the two however results in a further increase in the yield of  $\beta$ -lactam **493** (44%), negating any potential deleterious effects Xantphos may have singularly on the formation of product (Scheme 128).

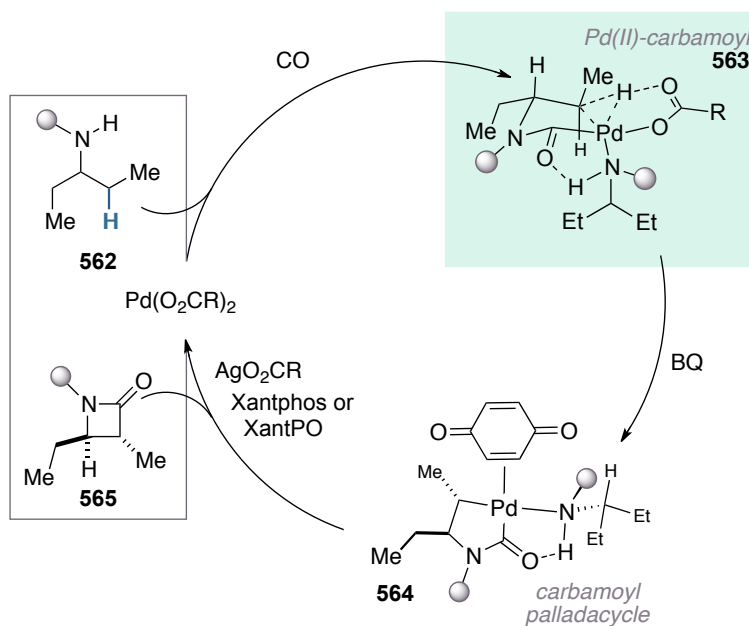
Along these lines, we believe that a carbamoyl-Pd intermediate **559**, previously hypothesized in the group<sup>429</sup>, could be the active species from which  $\beta$ -methylene C–H activation occurs. To test this, the carbamoyl chloride **560** of 3-aminopentane was prepared by Dr M. Nappi and treated with  $Pd(PPh_3)_4$

in toluene at 50 °C, which presumably undergoes oxidative addition forming a *de novo*  $Pd^{II}$ -carbamoyl complex **561** (Scheme 129). Pleasingly, the desired  $\beta$ -lactam **493** was obtained in 18% yield.



**Scheme 129** | Preparation of a *de novo*  $Pd^{II}$ -carbamoyl complex. Reaction conducted by Dr M. Nappi

Taken together, we propose that a simplified mechanism involves the likely activation of CO by  $Pd(OAc)_2$ , which engages the amine substrate **562** and generates a  $Pd$ -carbamoyl intermediate **563** (Scheme 130). Subsequent C–H activation at the  $\beta$ -methylene position leads to the formation of a 5-membered ring carbamoyl palladacycle **564**, which following the putative coordination of 1,4-benzoquinone undergoes reductive elimination of the product **565**. Oxidation of Xantphos or XantPO ligated  $Pd^0$  by  $AgOAc$  regenerates the active  $Pd^{II}$ -catalyst.



**Scheme 130** | Proposed mechanism for  $Pd$ -catalyzed methylene  $\beta$ -C–H carbonylation of alkylamines

## 2.4 Summary

This chapter has described the development of the first methylene  $\beta$ -C–H carbonylation of alkylamines to form  $\beta$ -lactams. Initial work by Dr K. Ozaki identified this novel reactivity, wherein

suitably disposed methylene  $\beta$ -C–H bonds undergo preferential C–H activation in the presence of traditionally more reactive methyl  $\gamma$ -C–H bonds, affording  $\beta$ -lactam products in high diastereoselectivities. Subsequent optimization undertaken alongside Dr J. Cabrera-Pardo identified reaction conditions that proved general across a wide range of substrates; the use of Xantphos as a ligand proving critical to the efficiency of the transformation. With the help of Dr M. Nappi, an extensive substrate scope was evaluated (>60 alkylamines), encompassing  $\alpha$ - and  $\beta$ -branched secondary amines, as well as benzylic and heteroaryl containing motifs. Most notably, high levels of regioselectivity could be obtained using simple amino-alcohol-derived substrates, culminating in the highly selective carbonylation of an amino alcohol containing four distinct methylene C–H bond environments. The resulting  $\beta$ -lactam products were shown to be amenable to a range of useful synthetic transformations including ring opening, reduction to the azetidine, as well as photochemical cleavage liberating the free (*NH*)-lactam. Finally, mechanistic studies led to the proposed intermediacy of a Pd-carbamoyl species, giving rise to this inimitable selectivity.

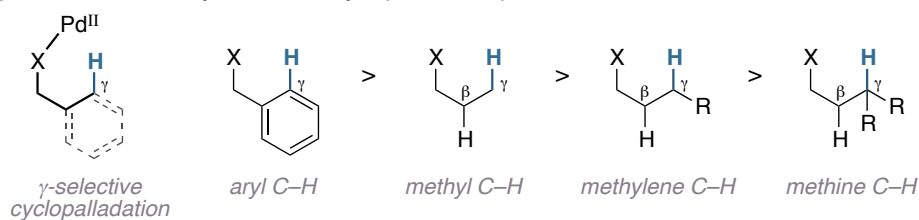
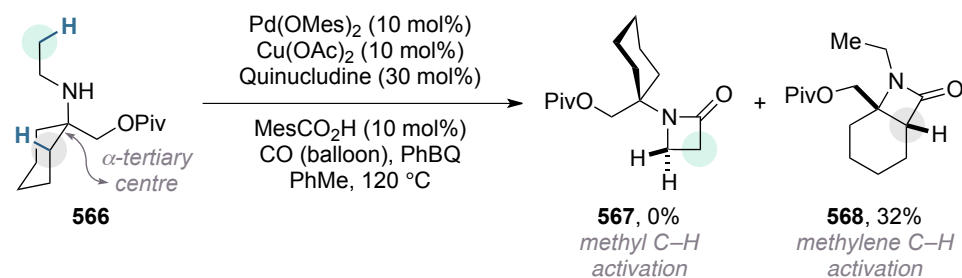
### 3 Selective carbonylation of methylene $\beta$ -C–H bonds in $\alpha$ -tertiary amines

#### 3.1 Previous work

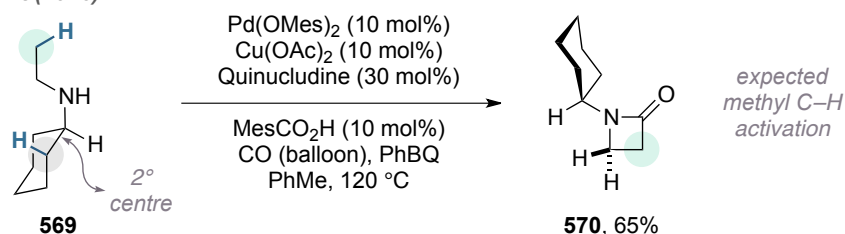
During the course of our investigations into the development of a general platform for the C–H carbonylation of alkylamines, Dr K. Hogg identified a remarkably unusual feature inherent to this activation mode.  $\alpha$ -Tertiary alkylamines (ATAs), containing both  $\beta$ -methyl and  $\beta$ -methylene C–H bonds, underwent exclusive activation at the traditionally less-reactive  $\beta$ -methylene position. Conventionally, C–H activation follows a well-established set of rules governing selectivity;  $C(sp^2)$ –H bonds are preferentially activated to  $C(sp^3)$ –H bonds, benzylic and allylic  $C(sp^3)$ –H bonds > methyl  $C(sp^3)$ –H bonds > methylene  $C(sp^3)$ –H bonds > methine  $C(sp^3)$ –H bonds (Scheme 131a)<sup>261,298</sup>. These observed selectivities are brought about by a combination of pre-association effects, M–C bond strengths, and sterics around the C–H activation transition states<sup>507</sup>.

Opportunely, it was found that upon subjecting pivalate-protected (1-(ethylamino)cyclohexyl)methanol amine **566** to conditions previously developed for methyl C–H bond carbonylation, in anticipation of methyl C–H activation of the *N*-ethyl substituent **567**, the 4,6-fused  $\beta$ -lactam product resulting from carbonylation of the methylene  $\beta$ -C–H bond in the cyclohexyl ring **568** was furnished in 32% yield (Scheme 131b). Importantly, the analogous *N*-(cyclohexyl)ethylamine substrate **569**, without the  $\alpha$ -tertiary centre, afforded the  $\beta$ -lactam **570** resulting from methyl  $\beta$ -C–H, in 65% yield (Scheme 131c)<sup>429</sup>.

## (a) traditional selectivity in classical cyclopalladation processes

(b)  $\alpha$ -tertiary amine C–H activation by Dr K. Hogg

## (c) Gaunt (2016)



**Scheme 131** | (a) Traditional selectivity for C–H activation. (b) C–H Activation of  $\alpha$ -tertiary amines by Dr K. Hogg. (c) C–H Activation of N-ethyl amines

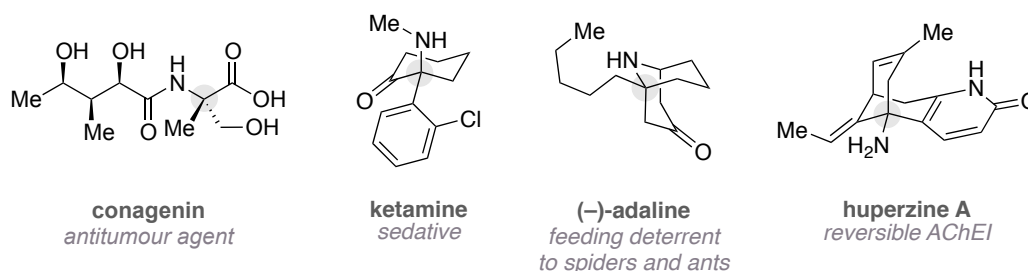
## 3.2 Project aims

Methods that allow the selective activation of inert C–H bonds have great potential in streamlining the synthesis of complex molecules. However, these molecules often contain multiple C–H bonds in subtly different electronic and spatial environments, rendering the development of catalytic methods that are able to target specific C–H bonds a formidable task. Through the use of a novel activation mode distinct from classical cyclopalladation, we have established a general methodology that enables the activation of  $\beta$ -C–H bonds in alkylamines to form complex  $\beta$ -lactam products. Remarkably, an ATA bearing both methyl and methylene  $\beta$ -C–H bonds showed an unprecedented preference of carbonylation at the traditionally less reactive methylene site.

The aim of this project was to establish a general protocol for the selective methylene  $\beta$ -C–H carbonylation of ATAs across a range of ring sizes. Furthermore, we sought to examine the functional group compatibility of the reaction and explore the selectivity against methylene  $\beta$ -C–H bonds in different environments, as well as against more reactive  $C(sp^2)$ -H bonds. In addition, we

aimed to elucidate the mechanism behind this unique selectivity and apply it towards the synthesis of more complex molecular targets.

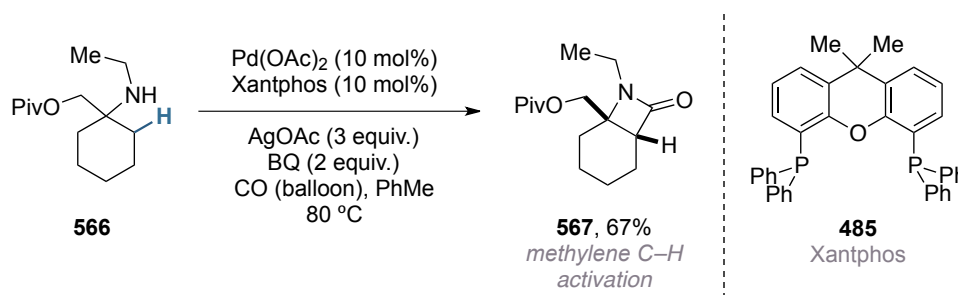
Given the importance of ATAs in natural products and pharmaceuticals (Figure 4), due in part to their unique physiochemical properties, coupled with the limited number of methods for their synthesis, we were keen to establish a methodology to functionalize these important molecular scaffolds<sup>508,509</sup>.



**Figure 4** | The importance of  $\alpha$ -tertiary amines (ATAs)

### 4.3 Results and discussion

As this unique selectivity appeared selective for methylene  $\beta$ -C–H bonds, we wanted to ascertain whether the methodology previously developed for methylene  $\beta$ -C–H carbonylation (Chapter 3) would prove more effective. Gratifyingly, upon subjection of the ATA **566** to the methylene C–H carbonylation conditions employing Xantphos, BQ and AgOAc, the fused  $\beta$ -lactam product **567** could be accessed in 67% yield, vitally, without any activation of the methyl  $\beta$ -C–H bond (Scheme 132). Significantly, previous efforts to carbonylate the methylene  $\beta$ -C–H bonds in cyclohexylamines without an  $\alpha$ -tertiary centre were unsuccessful under these conditions (Scheme 117, p 101).

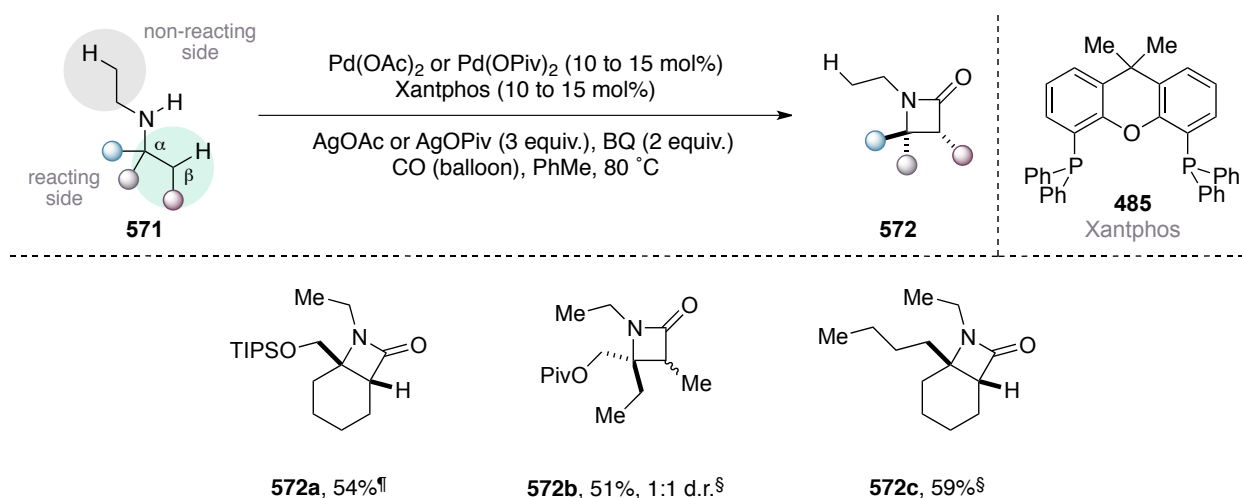


**Scheme 132** | Selective methylene  $\beta$ -C–H carbonylation of ATAs

Using these conditions, we were keen to assess a variety of substrates with differing substitution in the  $\alpha$ -position of the reacting side of the amine linkage, ensuring this unique reactivity was not the sole manifestation of the pivalate-protected alcohol (Scheme 133). The corresponding TIPS-protected alcohol **571a** was prepared by A. Alvarez-Pérez and subjected to the reaction conditions.

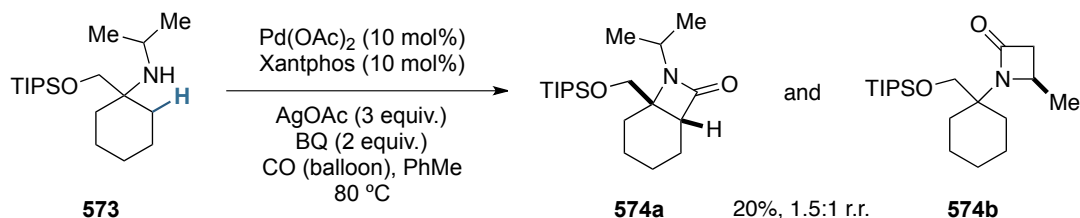


Pleasingly, the fused  $\beta$ -lactam product **572a** was furnished in a 54% yield. Importantly, the related acyclic pivalate-protected 2-(ethylamino)-2-ethylbutanol substrate **571b**, prepared by Dr K. Hogg, underwent smooth methylene  $\beta$ -C–H carbonylation, affording the  $\beta$ -lactam product **572b** in 51% yield (1:1 d.r.). Moreover, an unsubstituted *n*-butyl chain at the quaternary centre proved sufficient in delivering the fused  $\beta$ -lactam product **572c** in 59% yield, remarkably, without any activation of the exocyclic alkyl chain.



**Scheme 133** | Substrate scope for selective methylene  $\beta$ -C–H carbonylation of ATAs. <sup>¶</sup>Reaction conducted by A. Alvarez-Pérez. <sup>§</sup>Reaction conducted by Dr K. Hogg

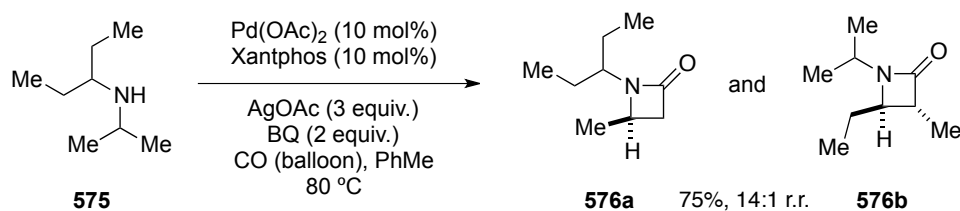
To test the limits of this selective methylene C–H activation methodology, TIPS-protected (1-(isopropylamino)cyclohexyl)methanol **573** was prepared by Dr K. Hogg and subjected to the reaction conditions (Scheme 134). The  $\alpha$ -branched isopropyl group significantly enhancing the reactivity of methyl C–H bonds towards activation and contains overall a 6:4 ratio of methyl to methylene C–H bonds – increasing the statistical chance of traditional methyl C–H activation. Although the carbonylation proceeded in a lower yield (20% total products), undoubtedly due to the significant steric crowding around the nitrogen, the reaction displayed considerable levels of selectivity, affording a 1.5:1 ratio of products **574a** and **574b** in favour of the methylene activated product.



**Scheme 134** | Selective methylene  $\beta$ -C–H carbonylation of N-isopropyl ATAs. Reaction conducted by Dr K. Hogg

In order to contextualize the significance of this selectivity, a competition experiment conducted by Dr J. Cabrera-Pardo using *N*-(isopropyl)pentan-3-amine **575**, notably without an  $\alpha$ -tertiary centre,

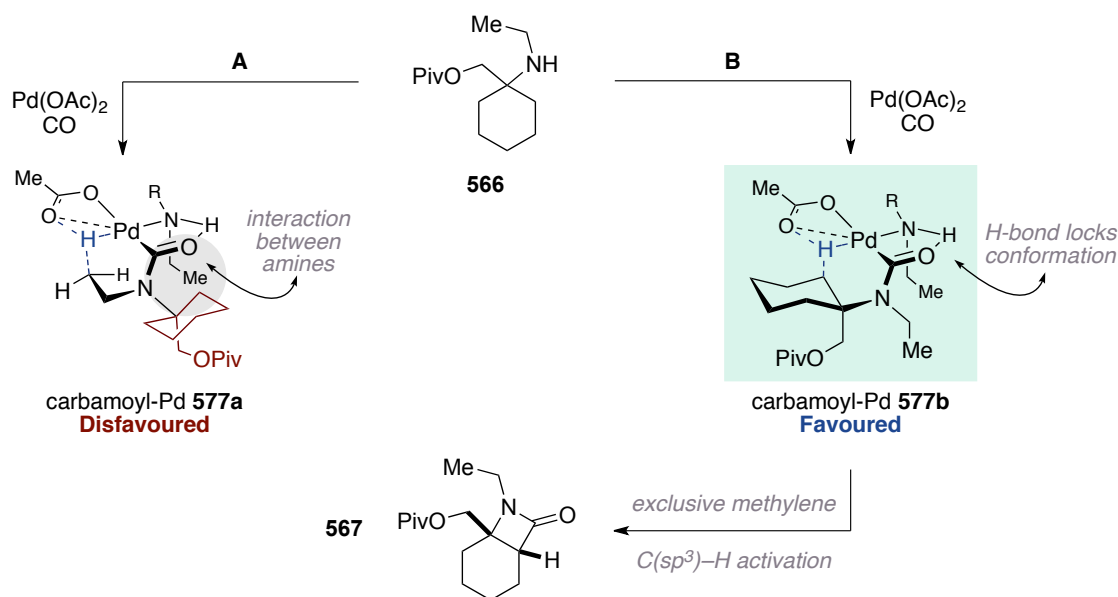
displayed a 14:1 selectivity in favour of activation of the methyl **576a** over the methylene  $\beta$ -C–H bonds **576b** (Scheme 135).



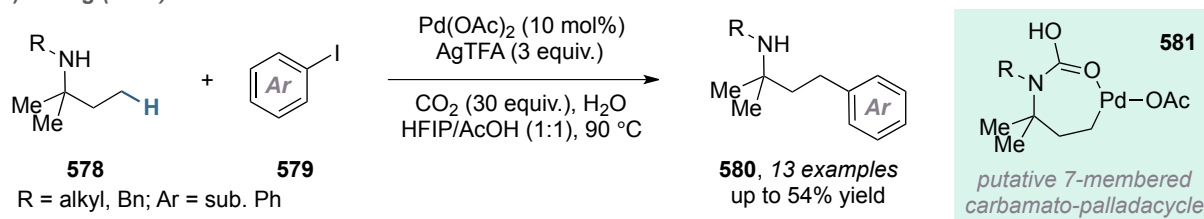
**Scheme 135** | Methylene  $\beta$ -C–H carbonylation of *N*-(isopropyl)pentan-3-amine. Reaction conducted by Dr J. Cabrera-Pardo

In order to rationalize this selectivity, we turned our attention to the mechanism of ATA carbonylation. Assuming that under identical reaction conditions the same proposed mechanism for  $\beta$  methylene C–H carbonylation is operative (Scheme 130), we reasoned that the unique selectivity most likely arises out of Curtin-Hammett control from the Pd-carbamoyl intermediate (Scheme 136a)<sup>510,511</sup>. Clearly, significant delocalization of the nitrogen lone pair into the carbamoyl intermediate renders its substituents in two distinct environments, akin to *cis*- and *trans*-amide isomers<sup>512</sup>. Consistent with previous studies, a key hydrogen bond between the carbamoyl oxygen and N–H of another Pd-bound amine is proposed to lock the relative conformation of the amide, facilitating C–H activation<sup>429</sup>. Along these lines, we propose that in order for activation of the methyl C–H bond to occur (pathway A), the bulky quaternary substituent would be displaced close to the other ligated amine, resulting in an unfavourable steric clash (**577a**). Accordingly, activation of the methylene  $\beta$ -C–H bond (pathway B) displaces the smaller ethyl group towards the ligated amine (**577b**). Moreover, the reduced selectivity observed in the case of protected (1-(isopropylamino)cyclohexyl)methanol **573** may result from poorer steric differentiation between the two Pd-carbamoyl intermediates caused by the larger isopropyl substituent. Additionally, we cannot rule out the possibility of a Thorpe-Ingold (angle compression) effect contributing to the selectivity exhibited by the reaction, though we doubt this effect alone is able to impart such a switch in reactivity<sup>513</sup>. In 2018, Young reported an elegant CO<sub>2</sub>-mediated  $\gamma$ -C(*sp*<sup>3</sup>)–H arylation of primary and secondary aliphatic amines **578** with aryl iodides **579** (Scheme 136b)<sup>514</sup>. Interestingly, the reaction proved remarkably selective for secondary alkyl ATAs, with arylation occurring exclusively on the more substituted side (**580**). Additionally, benzyl-derived ATAs proved resistant to competing C(*sp*<sup>2</sup>)–H arylation under the reaction conditions. In line with our findings, the authors propose that a more favourable conformation during C(*sp*<sup>3</sup>)–H activation is likely responsible for the high levels or selectivity **581**.

## (a) putative mechanistic rationale for the selective carbonylation of ATAs

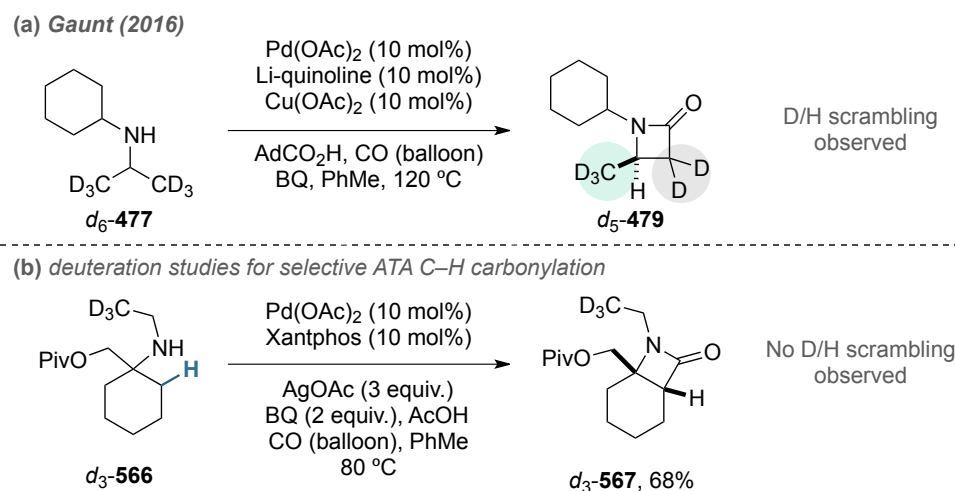


## (b) Young (2018)



**Scheme 136** | (a) Proposed mechanistic rationale for selective ATA  $\beta$ -C–H carbonylation. (b)  $\text{CO}_2$  Mediated Pd-catalyzed  $\gamma\text{-C}(\text{sp}^3)\text{-H}$  arylation of alkylamines

Previous mechanistic studies conducted by Dr B. Chappell revealed that amine directed methyl  $\beta$ -C–H bond activation to form  $\beta$ -lactams was reversible (Scheme 137a)<sup>429</sup>. Using *N*-(isopropyl- $d_6$ )cyclohexylamine  $d_6$ -**477**, significant D/H scrambling was observed in the  $\beta$ -lactam product  $d_5$ -**479**, implying that the two amine substituents undergo interconversion within the Pd-carbamoyl intermediate. However, according to our mechanistic hypothesis for ATA C–H activation, activation of the methyl  $\beta$ -C–H would be disfavoured due to the higher energy Pd-carbamoyl geometry. To test this, pivalate-protected (1-(ethyl-2,2,2- $d_3$ )aminocyclohexyl)methanol  $d_3$ -**566** was synthesized and subjected to the reaction conditions with one equivalent of AcOH (Scheme 137b). Pleasingly, no H/D scrambling was observed in the pendant deuterated ethyl substituent  $d_3$ -**567**.

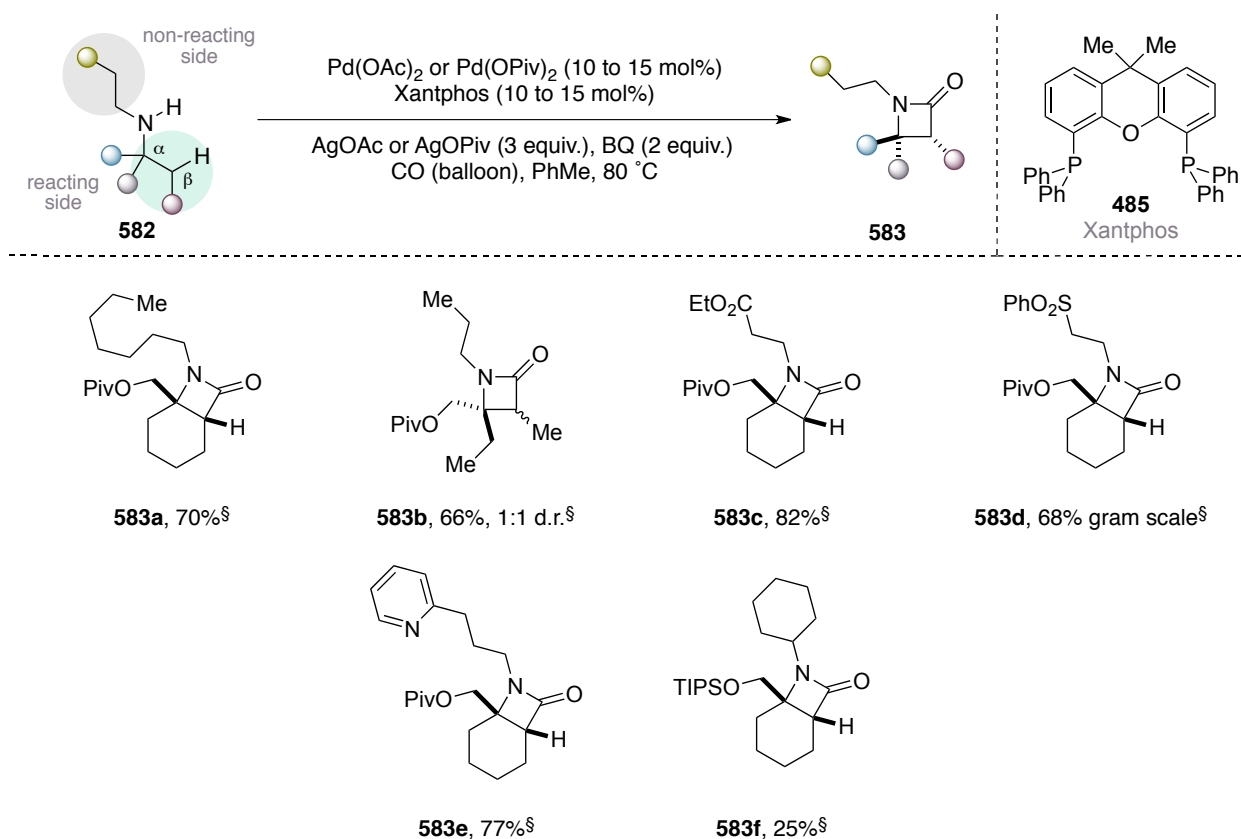


**Scheme 137** | (a) Reversible C–H activation of *N*-(isopropyl)cyclohexylamine. (b) Deuteration studies for selective ATA C–H carbonylation

Having demonstrated successfully that amines bearing an  $\alpha$ -tertiary centre undergo regioselective methylene  $\beta$ -C–H activation, we sought to investigate how other substituents on the non-reacting side of the amine affected the C–H activation process (Scheme 138). Pleasingly, no competing  $\gamma$ -C–H activation was observed in either *n*-heptyl or *n*-propyl containing amines **582a** and **582b**, affording the corresponding  $\beta$ -lactam products **583a** and **583b** in 70% and 66% yields respectively. Curiously,  $\beta$ -amino ester and  $\beta$ -phenyl sulfone-derived amines **582c** and **582d** underwent carbonylation to generate the products **583c** and **583d** in 82% and 68% yields respectively, the latter performed on a gram-scale. The corresponding 3-aminopentane-derived amino ester and sulfone without an  $\alpha$ -tertiary centre failed to undergo methylene  $\beta$ -C–H activation under the same reaction conditions. Moreover, (2-pyridyl)propyl amine **582e** underwent C–H activation to generate the  $\beta$ -lactam product **583e** in 77% yield, in stark contrast to the reactivity previously encountered using  $\alpha$ -secondary amines (Scheme 115). Impressively, bis-cyclohexyl-derived amine **582f**, containing two sets of nearly identical methylene C–H bonds, gave rise to a single  $\beta$ -lactam product **583f**, with activation occurring exclusively on more substituted side, albeit in a lower 25% yield.

Having established the generality of the transformation, we turned our attention towards previously intractable *N*-methylamines **584** (Scheme 139). Although *N*-methylamines are one of the most widely encountered groups amongst biologically active molecules<sup>515</sup>, their high reactivity towards transition metal reagents has often rendered them incompatible with many C–H activation methodologies<sup>336,516</sup>. In particular, the rapid oxidation of *N*-methylamines to the corresponding imine and subsequent nucleophilic attack, known as cross-dehydrogenative coupling (CDC), has been well-studied<sup>517–520</sup>. However, on the grounds that the geometry of the Pd-carbamoyl intermediate is locked, we reasoned that the reactive methyl group would be displaced remotely from the palladium

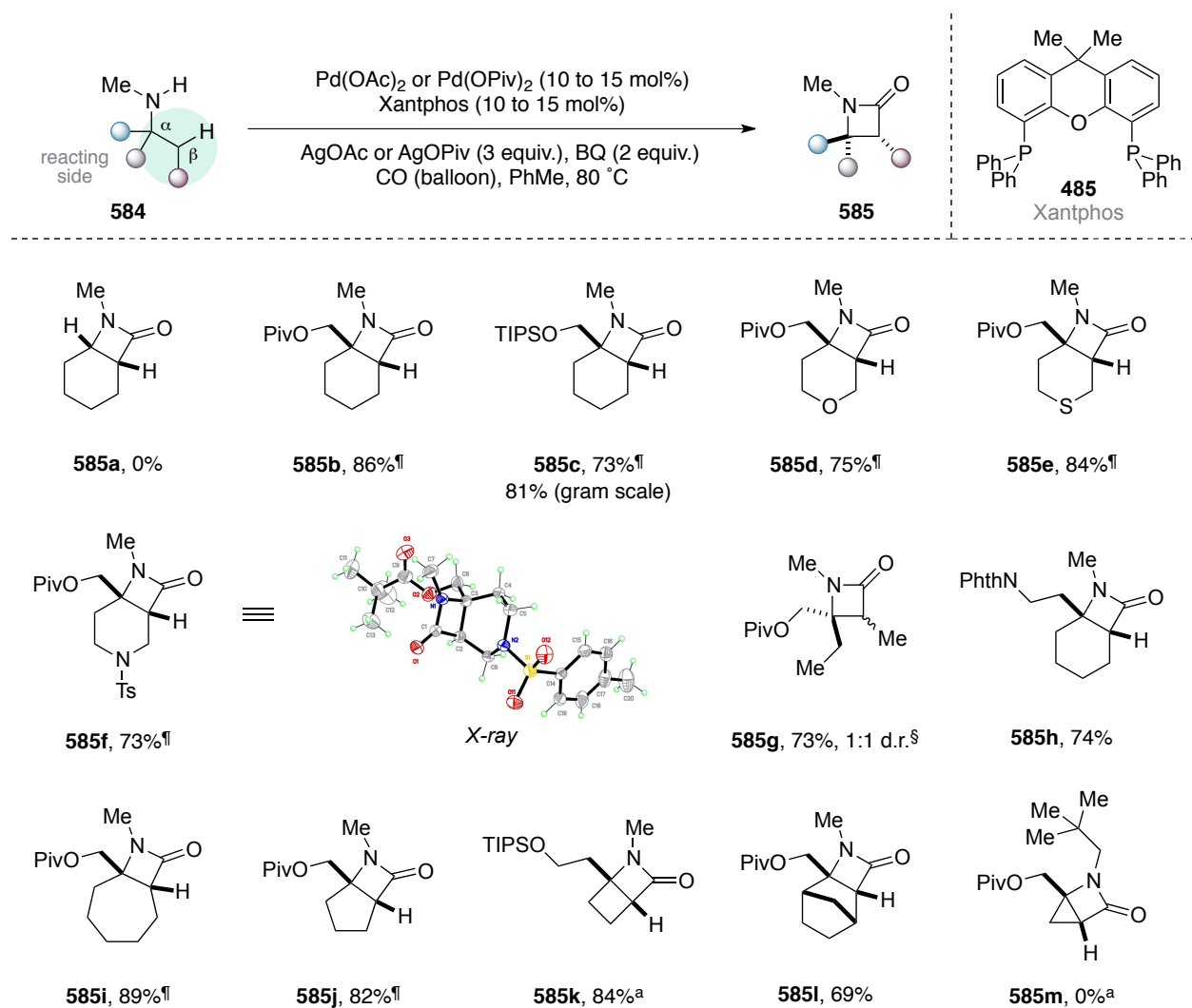
centre. To test the reactivity of *N*-methyl amines, *N*-methylcyclohexylamine **584a** was subjected to the C–H carbonylation conditions, critically, no  $\beta$ -lactam product **585a** was obtained and complete decomposition of the starting amine **585a** was observed (Scheme 136).



**Scheme 138** | Substrate scope for selective  $\beta$ -C–H carbonylation of ATAs. <sup>§</sup>Reaction conducted by Dr K. Hogg

On the other hand, both pivalate and TIPS-protected (1-(methylamino)cyclohexane)methanol **584b** and **584c** prepared by A. Alvarez-Pérez, bearing the important  $\alpha$ -tertiary centre, furnished the  $\beta$ -lactam products **585b** and **585c** in 86% and 73% yields respectively (Scheme 139). Due to the prevalence of *N*-methyl amines in pharmaceutical agents, A. Alvarez-Pérez and Dr K. Hogg set about further investigating the scope of this important carbonylation process. Given that  $\alpha$ -tertiary amino alcohols have proven particularly amenable towards methylene  $\beta$ -C–H activation, as well as their ready access from the corresponding amino acids, a series of heterocyclic substrates were prepared. Pleasingly, tetrahydropyran, tetrahydrothiopyran- and Ts-piperidine-derived substrates **584d–584f** underwent carbonylation in good yields, affording the products **585d–585f** in 75%, 84% and 73% yields respectively. Importantly, the corresponding acyclic  $\alpha$ -tertiary *N*-methyl amine **584g** furnished the product in 73% yield (1:1 d.r.). Significantly, the scope was not limited to protected hydroxymethylene substituents; phthalimide-protected 1-(2-aminoethyl)-*N*-methylcyclohexylamine **584h** proved a competent substrate, delivering the  $\beta$ -lactam product **585h** in 74% yield. We next turned our attention to examining the scope of methylene  $\beta$ -C–H carbonylation on different ring

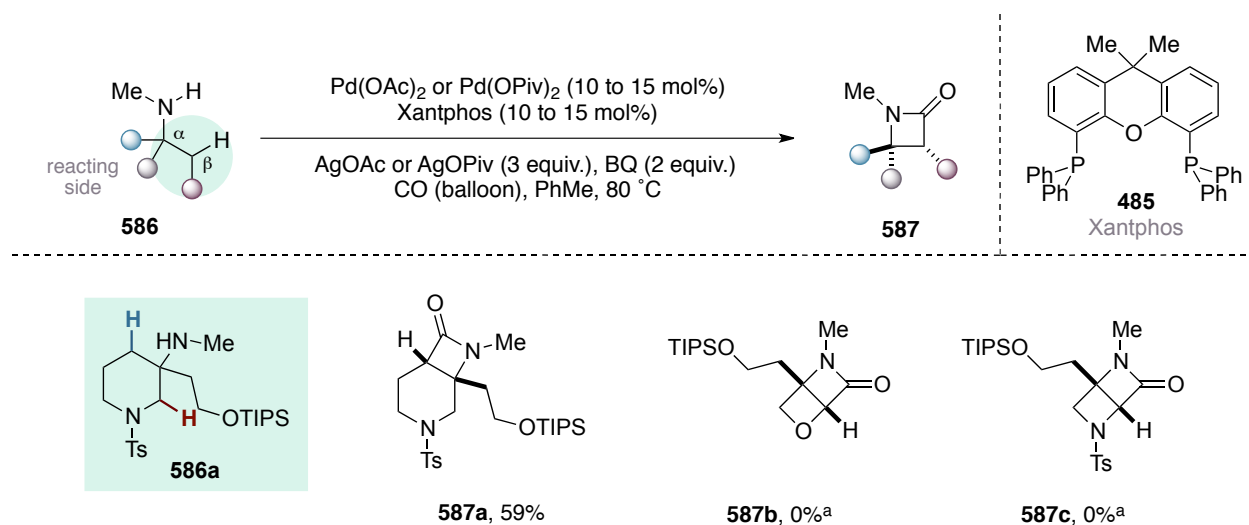
sizes. Remarkably, 4-, 5- and 7-membered rings **584i**–**584k** proved highly reactive under the reaction conditions despite the vast differences in C–C–C bond angle ( $\theta \approx 88^\circ$  to  $118^\circ$ )<sup>521</sup>. Most notably, the activation of protected (1-(methylamino)cyclobutane)methanol **584k** proceeded in 84% yield, generating a highly strained 4,4-fused  $\beta$ -lactam **585k** (~55 kcal/mol)<sup>522</sup>. Moreover, hindered norbornane-derived amine **584l** substrate afforded the tricyclic  $\beta$ -lactam **585l** in 69% yield. Unfortunately, the corresponding 3-membered ring ATA **584m** bearing an unreactive *N*-neopentyl substituent failed to deliver any of the desired  $\beta$ -lactam product **585m**, instead undergoing decomposition of the amine substrate.



**Scheme 139** | Substrate scope for selective methylene  $\beta$ -C–H carbonylation of ATAs. <sup>a</sup>Reaction conducted using  $\text{Pd}(\text{OPiv})_2$  (10 mol%) and AgOPiv (3 equiv.). <sup>¶</sup>Reaction conducted by A. Alvarez-Pérez. <sup>§</sup>Reaction conducted by Dr K. Hogg

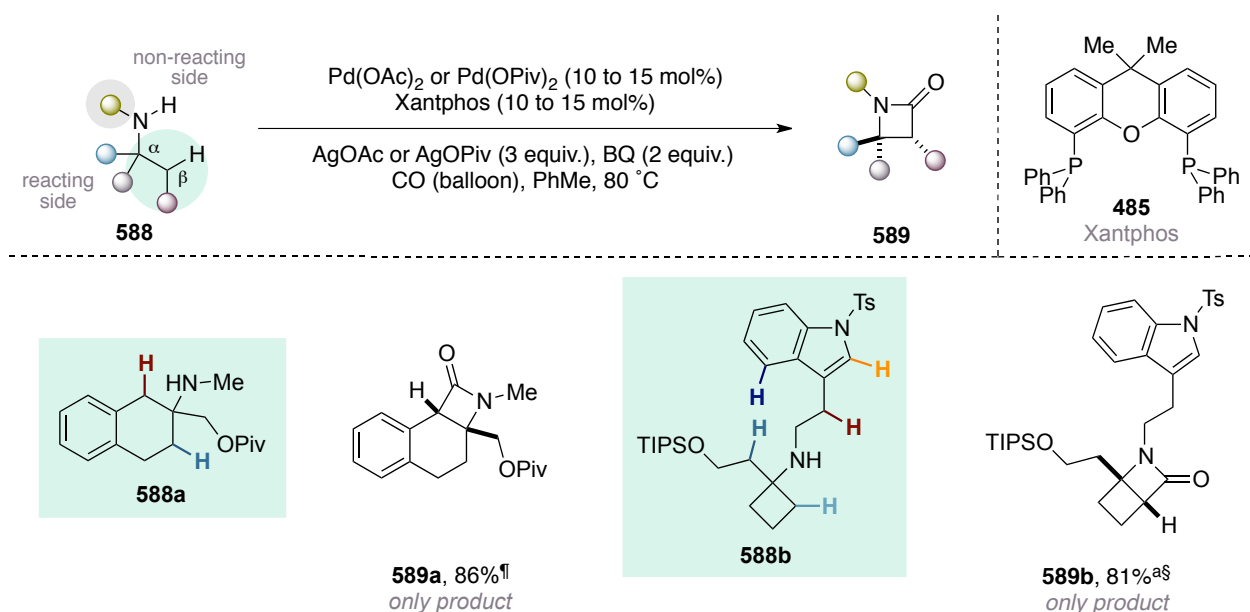
To test the limits of the selective  $\beta$ -C–H carbonylation methodology for ATAs bearing multiple reactive methylene  $\beta$ -C–H bonds, we prepared a number of substrates that could potentially form distinct  $\beta$ -lactam products **587** (Scheme 140). Along these lines, unsymmetrical 3-amino piperidine-derived ATA **586a** was synthesized and subjected to the reaction conditions. Pleasingly, a single  $\beta$ -

lactam product **587a** was furnished in 59% yield, resulting from the selective activation of the cyclic methylene C–H bond distal to the heteroatom. Based on this, we were keen to ascertain whether 3-amino oxetane and azetidine substrates **586b** and **586c** would deliver the desired fused  $\beta$ -lactam products, potentially accessing new heterocyclic motifs for use within drug-discovery platforms<sup>523–526</sup>. However, as the only cyclic C–H bonds present were adjacent to heteroatoms, we were doubtful of the efficiency of such a process. Perhaps unsurprisingly, neither the oxetane- nor azetidine-derived ATA afforded the desired  $\beta$ -lactam products **587b** and **587c**, instead undergoing decomposition in the case of oxetane-derived amine, or returning starting material in the case of azetidine.



**Scheme 140** | Substrate scope for selective methylene  $\beta$ -C–H carbonylation of ATAs. <sup>a</sup>Reaction conducted using  $\text{Pd}(\text{OPiv})_2$  (10 mol%) and  $\text{AgOPiv}$  (3 equiv.)

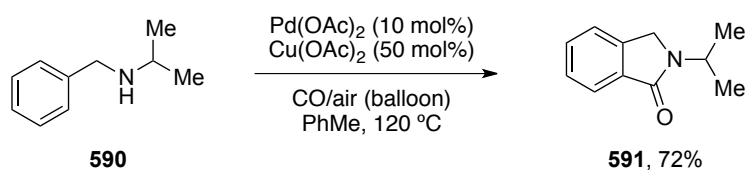
While heteroatoms served as useful tools to govern the selectivity for methylene  $\beta$ -C–H carbonylation, we sought to investigate the effect of other functional groups proximal to the reactive site. Previously, little discrimination was observed between alkyl and benzylic methylene C–H bonds (Scheme 118); however, 2-aminotetralin-derived amine **588a** prepared by A. Alvarez-Pérez afforded a single  $\beta$ -lactam product **589a** with activation occurring exclusively at the benzylic C–H bond in 86% yield (Scheme 141). Furthermore, tryptamine-derived cyclobutyl-ATA **588b** prepared by Dr K. Hogg underwent exclusive activation on the cyclobutyl ring to generate the fused 4,4- $\beta$ -lactam product **589b** in 81% yield, demonstrating a noteworthy level of selectivity for the generation of a highly strained product in favour of facile  $\text{C}(\text{sp}^2)$ -H activation of the electron-rich indole (Scheme 141)<sup>527</sup>.



**Scheme 141** | Substrate scope for selective methylene  $\beta$ -C–H carbonylation of ATAs. <sup>a</sup>Reaction conducted using  $\text{Pd}(\text{OPiv})_2$  (10 mol%) and AgOPiv (3 equiv.). <sup>†</sup>Reaction conducted by A. Alvarez-Pérez. <sup>§</sup>Reaction conducted by Dr K. Hogg

As a consequence of the high reactivity of  $\text{C}(\text{sp}^2)$ -H bonds towards C–H activation methodologies, examples of selective Pd-catalyzed methylene  $\beta$ -C–H activation in the presence of suitably disposed  $\gamma$ - $\text{C}(\text{sp}^2)$ -H bonds are exceedingly rare. In fact, the previously described methylene  $\beta$ -C–H carbonylation of benzyl substituted secondary amines **590** by Orito generated the corresponding benzolactams **591** in good yields (Scheme 142)<sup>488,489</sup>. To this end, we were keen to establish whether ATAs bearing a benzyl group on the unsubstituted side would succumb to a similar fate, given the high selectivity thus far observed for activation of the  $\alpha$ -tertiary substituent.

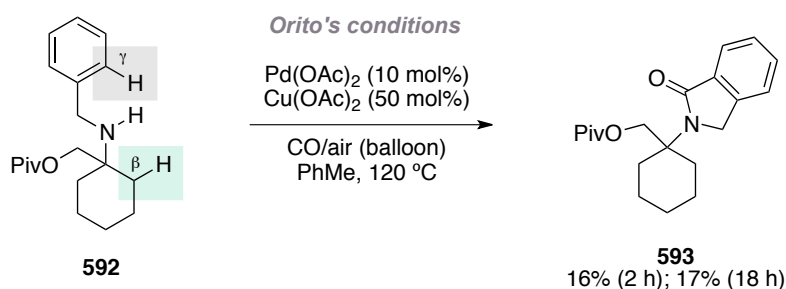
Orito (2006)



**Scheme 142** | Pd-catalyzed  $\text{C}(\text{sp}^2)$ -H carbonylation of benzylamines

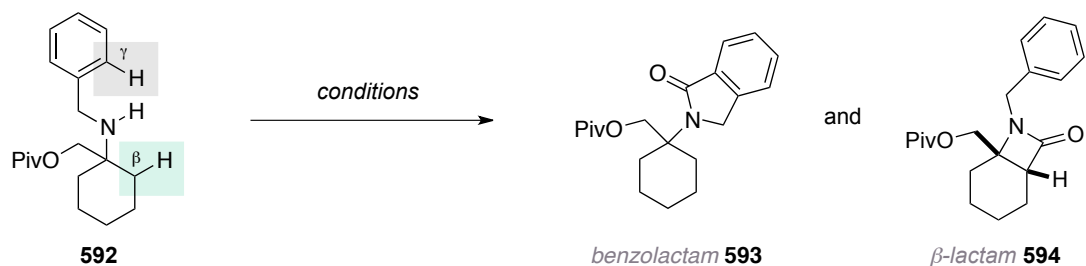
To benchmark the selectivity of the our selective ATA  $\beta$ -C–H carbonylation process, Dr K. Hogg subjected pivalate-protected (1-(benzylamino)cyclohexane)methanol **592** to the reaction conditions developed by Orito, employing catalytic  $\text{Pd}(\text{OAc})_2$  and  $\text{Cu}(\text{OAc})_2$  under an atmosphere of CO/air at 120 °C, for the  $\text{C}(\text{sp}^2)$ -H carbonylation of similar *N*-alkylbenzylamines (Scheme 143). Predictably, the benzolactam product **593** was formed exclusively in a diminished 16% yield after 2 hours, presumably via classical 5-membered cyclopalladation. Little improvement to the yield was observed over a longer 18-hour period. Critically however, no  $\beta$ -lactam was observed in the reaction mixture.





**Scheme 143** | Pd-catalyzed carbonylation of *N*-benzyl ATAs under Orito's conditions. Reaction conducted by Dr K. Hogg

Extraordinarily, when Dr K. Hogg subjected *N*-benzyl ATA **592** to conditions designed for ATA  $\beta$ -C–H carbonylation, a mixture of lactam products **593** and **594** was obtained in a much-improved 83% yield, markedly, in a 2.2:1 ratio in favour of the methylene activated  $\beta$ -lactam product **594** (Table 15, entry 1).



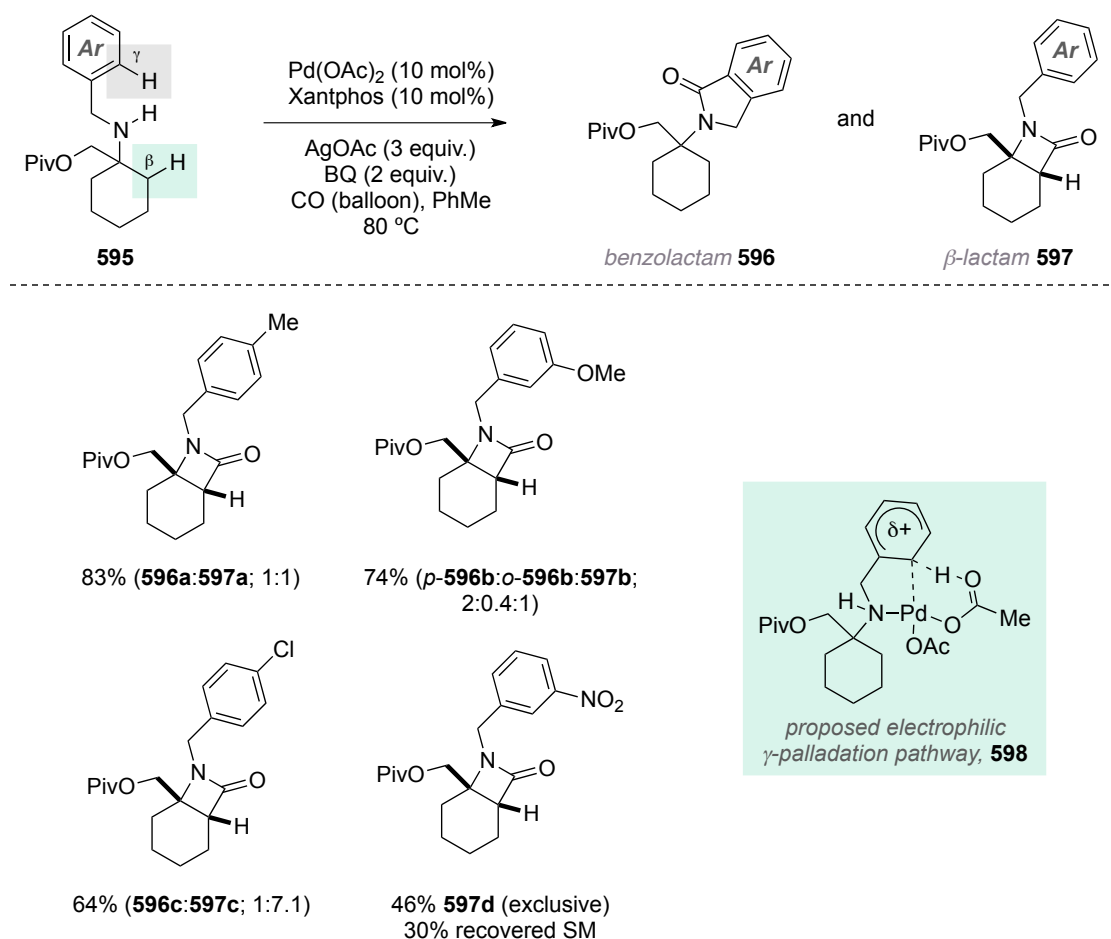
Entry	Temp. (°C)	Conditions	Yield (%) <sup>a</sup> ( <b>593</b> : <b>594</b> )
1 <sup>§</sup>	80	$\text{Pd}(\text{OAc})_2$ (10 mol%), Xantphos (10 mol%) AgOAc (3 equiv.), BQ (2 equiv.) CO (balloon), PhMe	83 (1:2.2)
2 <sup>§</sup>	120	$\text{Pd}(\text{OAc})_2$ (10 mol%), Xantphos (10 mol%) AgOAc (3 equiv.), BQ (2 equiv.) CO (balloon), PhMe	42 (9.5:1)
3 <sup>§</sup>	80	$\text{Pd}(\text{OAc})_2$ (10 mol%), AgOAc (3 equiv.) BQ (2 equiv.), CO (balloon), PhMe	trace
4 <sup>§</sup>	80	$\text{Pd}(\text{OAc})_2$ (10 mol%), AgOAc (3 equiv.) CO (balloon), PhMe	0%
5 <sup>§</sup>	120	$\text{Pd}(\text{OAc})_2$ (10 mol%), AgOAc (3 equiv.) CO/air (balloon), PhMe	25% (1:0)
6 <sup>§</sup>	80	$\text{Pd}(\text{OAc})_2$ (10 mol%), $\text{Cu}(\text{OAc})_2$ (50 mol%) CO/air (balloon), PhMe	0%
7 <sup>§</sup>	80	$\text{Pd}(\text{OAc})_2$ (10 mol%), $\text{Cu}(\text{OAc})_2$ (50 mol%) BQ (2 equiv.), CO/air (balloon), PhMe	0%
8 <sup>§</sup>	120	$\text{Pd}(\text{OAc})_2$ (10 mol%), $\text{Cu}(\text{OAc})_2$ (50 mol%) BQ (2 equiv.), CO/air (balloon), PhMe	13% (1:0)
9 <sup>§</sup>	120	$\text{Pd}(\text{OAc})_2$ (10 mol%), Xantphos (10 mol%) $\text{Cu}(\text{OAc})_2$ (50 mol%), BQ (2 equiv.) CO/air (balloon), PhMe	56% (1:0)

**Table 15** | Evaluation of reaction conditions for the Pd-catalyzed C–H carbonylation of *N*-benzyl ATAs. <sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane. <sup>§</sup>Reaction conducted by Dr K. Hogg

Intriguingly, when the reaction was performed at 120 °C the selectivity was reversed in favour of the benzolactam product **593** (9.5:1 r.r.), albeit in a lower 42% yield (Table 15, entry 2). Prominently, a

screen of reaction conditions revealed that a combination of Xantphos, AgOAc and BQ are required for  $\beta$ -lactam **594** formation, for the substitution or removal of any one component either led to no conversion to the product or exclusive formation of benzolactam **593** (Table 15, entries 3–9). Taken together, these results reveal a fascinating and unprecedented synergistic effect between ligand, oxidant and additive working together to overcome inherent substrate controlled selectivity.

In contrast to the work of Orito, wherein little selectivity was observed for the C( $sp^2$ )–H carbonylation of electronically distinct dibenzylamines **595**, we found that modifying the electronics of the benzyl group in ATAs had a profound effect on the selectivity (Scheme 144). In general, amines containing electron-rich substituents favoured C( $sp^2$ )–H activation of the benzyl group; *p*-methylbenzyl amine **595a** furnishing a 1:1 mixture of  $\beta$ -lactam/benzolactam **597a/596a** in 83% yield, and *m*-methoxybenzyl amine **595b** delivering a 1:2:0.4  $\beta$ -lactam:*p*-lactam:*o*-lactam **597b/p-596b/o-596b** mixture of regioisomers in 74% yield.

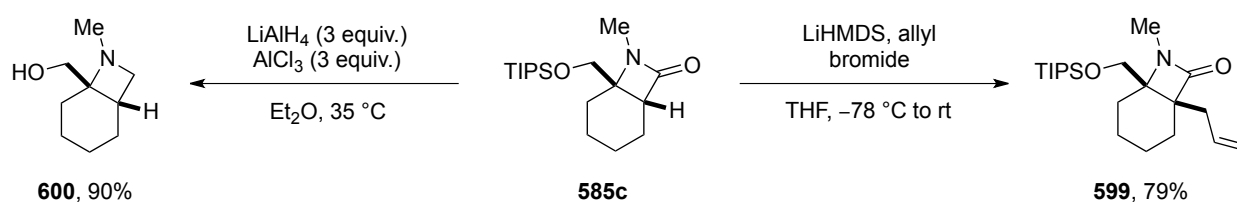


**Scheme 144** | Selective Pd-catalyzed C–H carbonylation of *N*-benzyl ATAs

On the other hand, electron-deficient *p*-chlorobenzyl amine **595c** underwent more facile C( $sp^3$ )–H activation, affording a 7.1:1 mixture of  $\beta$ -lactam/benzolactam **597c/596c** in 64% yield (Scheme 144).

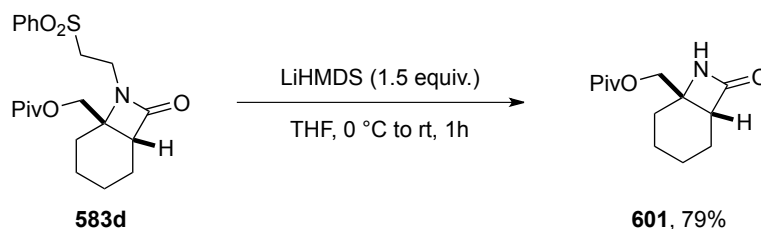
Moreover, *m*-nitrobenzyl amine **595d** exclusively afforded the  $\beta$ -lactam product **597d** without competing C( $sp^2$ )–H carbonylation, albeit in a moderate 46% yield. These results strongly indicate that C( $sp^2$ )–H activation occurs via an electrophilic palladation pathway **598**, whereby partial positive charge develops on the aromatic ring during the C–H activation transition state<sup>493</sup>.

The hindered  $\beta$ -lactam products generated from ATAs were found to undergo a series of potentially useful chemical transformations (Scheme 145). Alkylation using allyl bromide proved successful in delivering the fully substituted  $\beta$ -lactam **599** with vicinal all-carbon quaternary centres in 79% yield and complete retention of stereochemistry. Furthermore, reduction using LiAlH<sub>4</sub> and AlCl<sub>3</sub> afforded the corresponding bicyclic azetidiny alcohol **600** in 90% yield.



**Scheme 145** | Functionalization of bicyclic  $\beta$ -lactam products

Based on a report by Weinreb<sup>528</sup>, ethyl sulfone-derived  $\beta$ -lactam **583d** could be deprotected to the free (*NH*)-lactam **601** via a retro-Aza-Michael addition using LiHMDS in a good 79% yield (Scheme 146), offering a complementary strategy to the previously described photolabile nitrobenzyl group (Scheme 126).



**Scheme 146** | Retro-Aza-Michael deprotection of sulfonyl ethyl  $\beta$ -lactams. Reaction conducted by Dr K. Hogg

### 3.4 Summary

The work in this chapter has described the development of a remarkably selective methylene  $\beta$ -C–H carbonylation of  $\alpha$ -tertiary amines (ATAs), delivering synthetically versatile  $\beta$ -lactams in high yields. This methodology enables the C–H carbonylation of traditionally less-reactive methylene C–H bonds in the presence of more reactive methyl C–H bonds and C( $sp^2$ )–H bonds. We believe that the high levels of selectivity result from the unique properties of the bulky ATA motif, whereby the large tertiary amine substituent is placed close to the Pd-centre due to steric clashing between the carbamoyl and ligated amine substituents. As a result, a diverse range of functional groups that

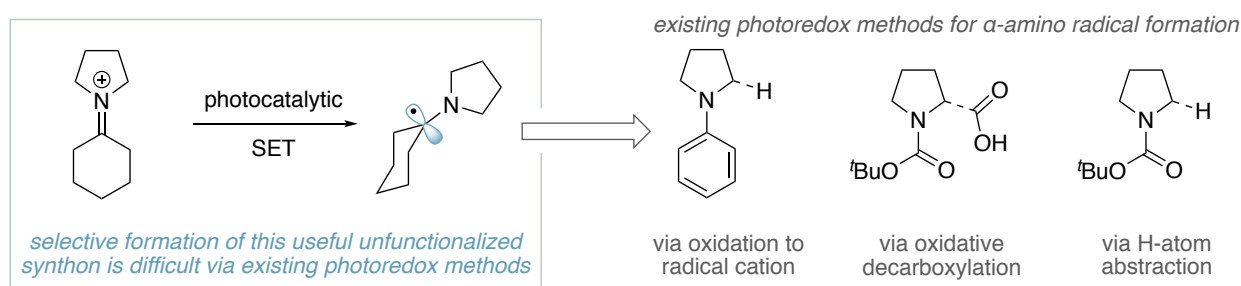
previously proved incompatible with methylene  $\beta$ -C-H carbonylation, including simple esters, sulfones and heteroaromatics, were tolerated in good yields. Notably, an impressive range of ring sizes were successfully accommodated under the reaction conditions, providing a simple route to access strained bicyclic  $\beta$ -lactam products. Moreover, the reaction was capable of distinguishing between similar cyclic methylene C-H bonds, activating selectively at benzylic C-H bonds and positions remote from heteroatoms. Using this methodology, a range of useful heterocyclic scaffold were synthesized and further derivatized, affording free (*NH*)-lactams, azetidines, and fully substituted  $\beta$ -lactam products.

## 4 Photocatalytic multicomponent synthesis of tertiary alkylamines

### 4.1 Introduction

$\alpha$ -Amino radicals are an emerging technology in the arsenal of reactive intermediates used in the day-to-day synthesis of complex amines<sup>367</sup>. The renaissance of photoredox catalysis over the last decade has ultimately led to an ever-increasing number of complex amine syntheses using these important entities (Section 1.4). Despite the significance of these transformations, the overwhelming majority of reactions generate  $\alpha$ -amino radicals via fragmentation (*vide supra*) and oxidative pathways: deprotonation of an amine radical cation or hydrogen atom transfer (HAT) directly via a suitable mediator (i.e. quinuclidine<sup>•+</sup>) (Scheme 147).

Problematically, oxidative pathways are inherently susceptible to issues of selectivity where multiple  $\alpha$ -hydrogen environments exist around the amine, none more so than for complex tertiary amines. In particular,  $\alpha$ -amino radicals derived from tertiary amines bearing different substituents regularly occur with unpredictable regiocontrol due to a balance of both kinetic and thermodynamic deprotonation<sup>529</sup>. On the other hand, reductive methods for accessing  $\alpha$ -amino radicals are far-less common, however, occur regiospecifically via the single electron reduction of a C=N bond (Scheme 144)<sup>530</sup>.

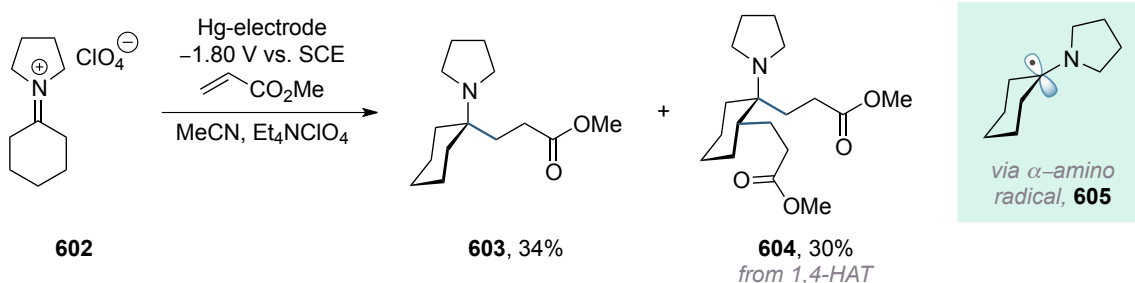


**Scheme 147** | Common photoredox-based strategies for the generation of  $\alpha$ -amino radicals

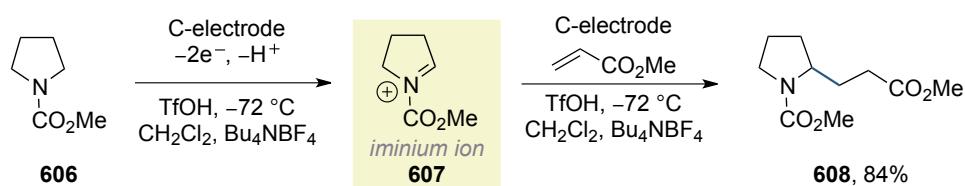
An early report by Kunai in 1983 detailed the electrochemical reduction and subsequent C–C bond coupling of tetrasubstituted alkyl iminium salts **602** (Scheme 148a)<sup>531</sup>. Problematically, the formed  $\alpha$ -amino radicals **605** were prone to polymerization and proved poorly selective even in the presence of electrophilic alkenes (**603**). Furthermore, the resulting alkyl radicals often underwent concomitant 1,4-HAT and subsequent radical addition to excess alkene (**604**), resulting in a complex mixture of products. In 2002, Yoshida reported the electrochemical reductive coupling of acyl iminium ions **607** ( $E_{1/2}^{\text{red}} = -0.85$  V vs. Ag/AgCl (MeCN) in  $\text{Bu}_4\text{NBF}_4/\text{CH}_2\text{Cl}_2$ ), formed through the oxidation of *N*-

acyl amines **606**, with electrophilic alkenes (Scheme 148b)<sup>532</sup>. Due to high levels of competing dimerization, the reactions were conducted at low temperature ( $-78\text{ }^{\circ}\text{C}$ ) with large excesses of alkene (5 to 8 equiv.) (**608**).

## (a) Kunai (1983)



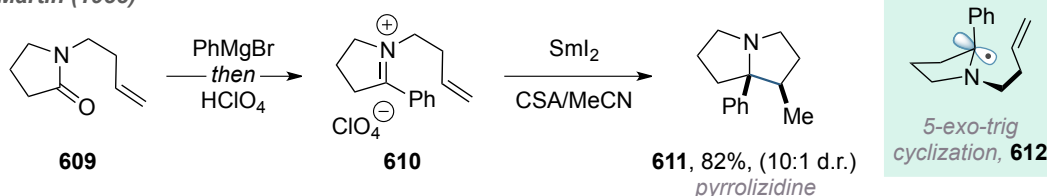
## (b) Yoshida (2002)



**Scheme 148** | (a) Electrochemical reduction of alkyl iminium ions. (b) Electrochemical reduction of *N*-acyl iminium ions

Due to their high reduction potentials (*vide infra*), a more traditional approach to the single electron reduction of alkyl substituted imines and iminium ions has been accomplished using strong stoichiometric reductants. In 1988, Martin reported the  $\text{SmI}_2$ -mediated reduction of iminium perchlorates **610**, prepared from the corresponding lactams **609**, for the synthesis of *N*-heterocycles **611** (Scheme 149)<sup>533</sup>. Subjection of  $\delta,\epsilon$ -unsaturated iminium salts to single electron reduction formed the  $\alpha$ -amino radical, which subsequently underwent facile intramolecular 5-*exo*-trig cyclization **612**. Additional single electron reduction of the resulting alkyl radical and protonation of the carbanion by CSA led to the formation of pyrrolizidine and indolizidine rings in moderate to good yields. More recent advances have employed the single-electron reductive coupling of reactive imine equivalents (acyl iminiums, oximes, hydrazine and nitrones) and activated alkenes using  $\text{SmI}_2$ <sup>534</sup>,  $\text{Ti}^{\text{III}}$ <sup>535</sup>, as well as the arylation of benzaldiminium ions using Ni-catalysis<sup>536</sup>.

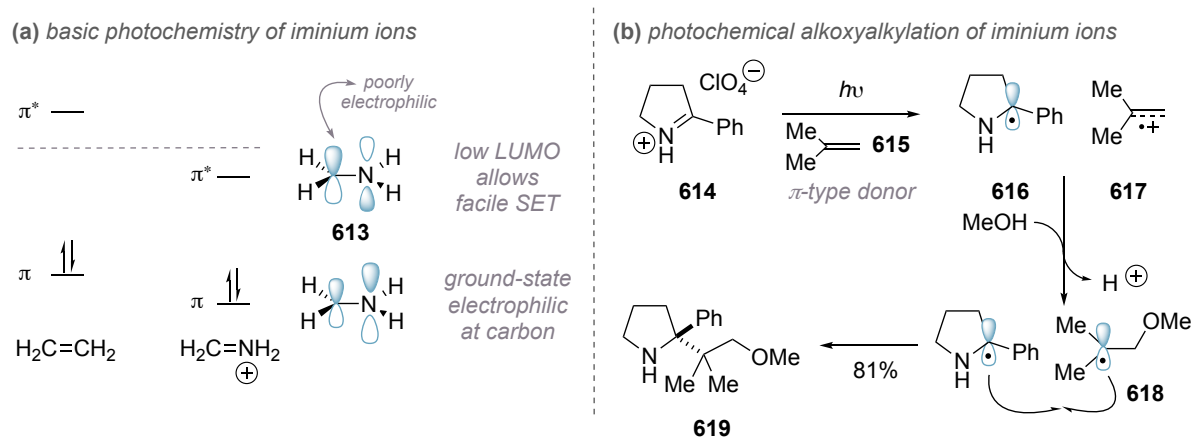
## Martin (1988)



**Scheme 149** |  $\text{SmI}_2$ -mediated reduction/cyclization of alkyl iminium ions

During the late 1970s and 1980s, Mariano detailed several reports on the single electron transfer mechanisms in photochemical transformations of iminium ions<sup>537,538</sup>. Iminium ions possess only one

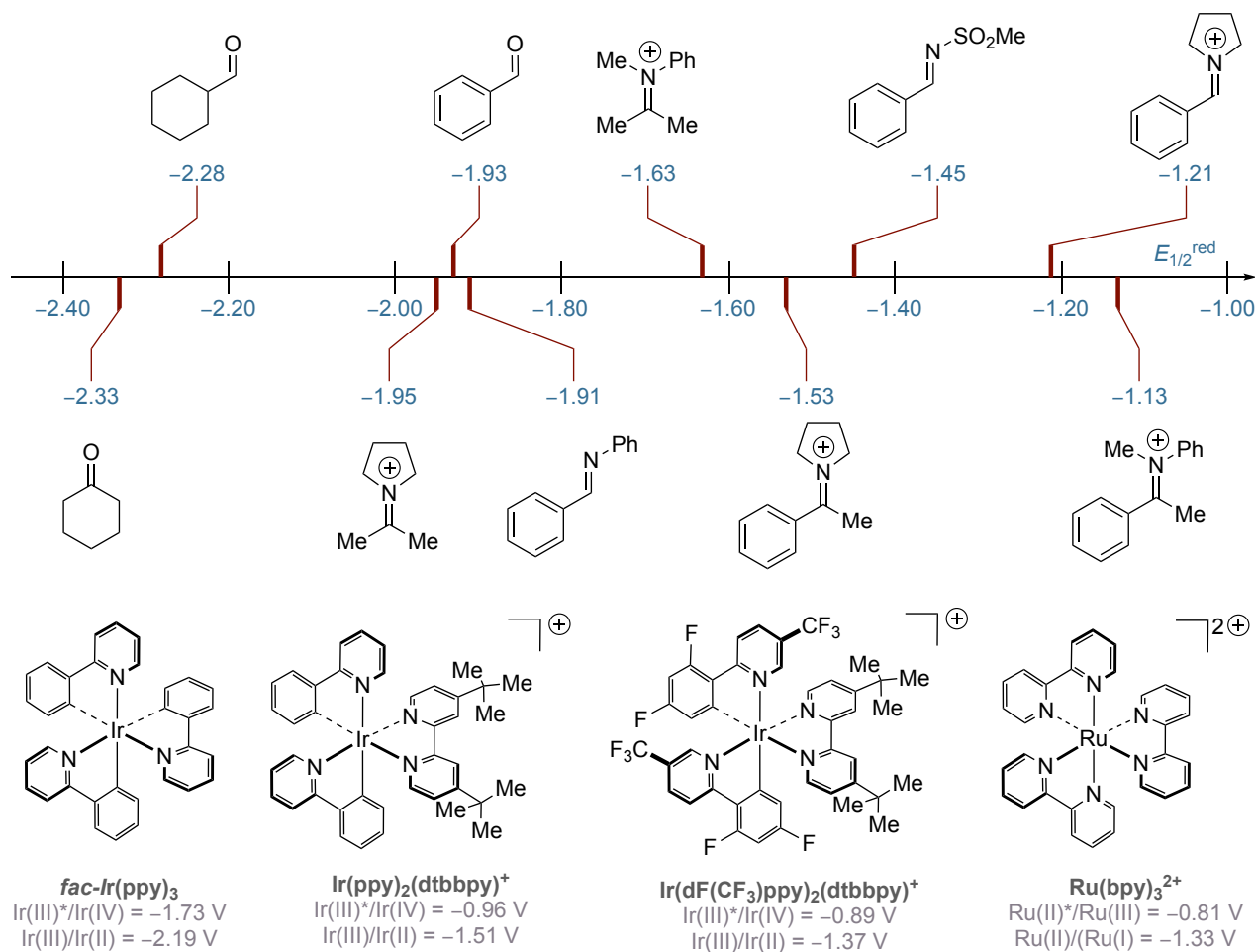
photochemical transition,  $\pi - \pi^*$ , which occurs primarily in the UV and visible regions similar to alkenes (Scheme 150a). However, unlike simple alkenes the significant delocalized positive charge in iminium ions lowers the energies of both the HOMO and LUMO. In fact, the low-lying LUMO **613** renders iminium ions particularly susceptible to single electron reduction to form  $\alpha$ -amino radicals (*vide supra*)<sup>539</sup>.



**Scheme 150** | (a) Basic photochemistry of iminium ions. (b) Photochemical alkoxyalkylation of iminium ions

Calculations, taking into account excited-state energies and ground state reduction potentials, suggest that excited state iminium ions should be ideal acceptors in electron transfer initiated photochemical processes<sup>540</sup>. Indeed, free energies for electron transfers from both ground-state  $\pi$ -type (alkenes and aromatics) and n-type (ethers) donors ( $E_{1/2}^{\text{ox}} < \text{ca. } +2.6 \text{ V}$ ) to singlet excited state iminium ions are calculated to be extremely exergonic [calculated according to Weller<sup>541</sup>;  $\Delta G_{\text{ET}}$  (2-phenyl-1-pyrrolinium perchlorate): THF =  $-23.0 \text{ kcal/mol}$ ; isobutylene =  $-13.8 \text{ kcal/mol}$ ; toluene =  $-36.8 \text{ kcal/mol}$ ]. In fact, rate constants for the quenching of excited state iminium ions with electron-rich alkenes occur near the diffusion-controlled limit (*ca.*  $1 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ ). A prototypical reaction involves the reductive alkoxyalkylation of 2-phenyl-1-pyrrolinium perchlorate **614** with isobutylene **615** and methanol (Scheme 150b)<sup>539</sup>. Excitation of the iminium ion to the singlet-excited state triggers an intermolecular electron transfer from isobutylene resulting in the formation of an  $\alpha$ -amino radical **616** and distonic isobutylene radical cation **617**, which is subsequently trapped by methanol at the least-hindered terminus **618**<sup>556</sup>. Radical-radical coupling affords the  $\alpha$ -alkoxyalkylated product **619** in good yield. Broadly speaking, this reaction exemplifies a much more general class of electron transfer initiated processes activated via loss of an electrofugal group from the  $\beta$ -position of a radical cation. To this end, the inter- and intramolecular alkenylation and benzylation of iminium ions with loss of  $\text{H}^+$ <sup>(542–546)</sup>, as well as the addition of allyl and benzyl silanes<sup>542,544,547–549</sup>, has been extensively reported. A recent report by Orfanopoulos has explored photoinduced electron transfer for the arylation and alkenylation of aza[60]fullerene iminium ions<sup>550</sup>.

Studies by Arnold<sup>551</sup>, and Andrieux and Savéant<sup>552,553</sup>, revealed that the half-wave reduction potentials of iminium salts shift to more positive values with increasing conjugation ( $E_{1/2}^{\text{red}} = -1.95$  to  $-0.84$  V vs. SCE in acetonitrile) (Scheme 151). In cases where significant stabilization occurs via conjugating substituents, the  $\alpha$ -amino radicals possess sufficiently long lifetimes ( $\sim 100$  ms) to be detected by EPR-spectroscopy<sup>552</sup>. As a result of the need for harsh stoichiometric reductants, complementary strategies that can effectively harness the reactivity of  $\alpha$ -amino radicals from C=N bonds under mild conditions would be of significant interest to the synthetic chemistry community.



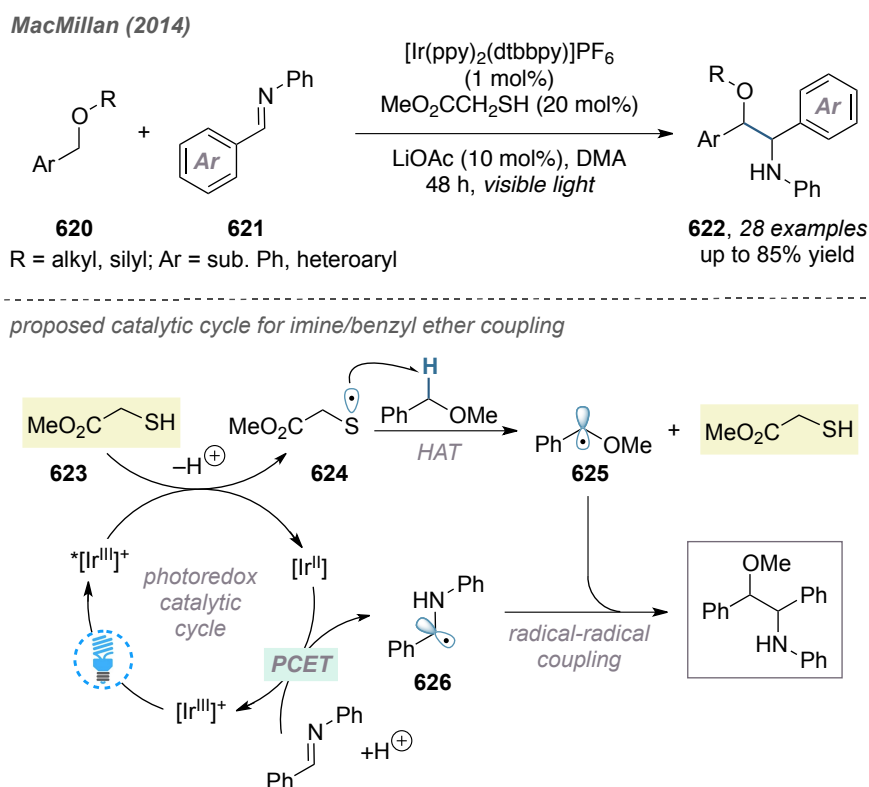
**Scheme 151** | Reduction potentials of selected C=X (X = O, N)<sup>552,554</sup> bond equivalents and common photocatalysts<sup>359,360</sup>. Values measured in V vs SCE.

Over the past two decades, photoredox catalysis has emerged as a mild alternative for the generation of radical intermediates via single electron transfer (Section 1.4). Although significant progress has been made in this area, the majority of excited photocatalysts, or their reduced forms, are not capable of reducing imines or iminium ions to the corresponding  $\alpha$ -amino radicals (Scheme 151). To combat this, several reports implement the use of Brønsted or Lewis acids in order to promote single electron transfer. In particular, the use of Brønsted acid facilitates PCET, whereby simultaneous transfer of a



proton and an electron enables the reduction of compounds with very low reduction potentials<sup>420</sup>; however, the scope of imines and coupling partners remains extremely limited.

In 2014, Macmillan detailed the first example of photocatalytic  $\alpha$ -amino radical generation via single electron reduction of an *N*-benzylideneanilines **621**, which efficiently coupled with benzylic ethers **620** to form a variety of  $\beta$ -amino ether products **622** (Scheme 152)<sup>555</sup>.

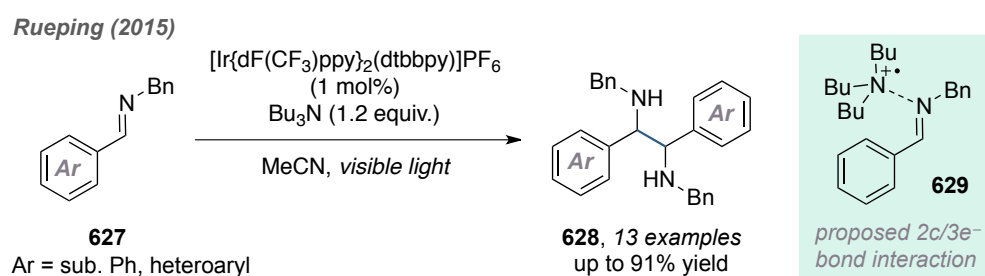


**Scheme 152** | Thioglycolate-mediated photocatalytic coupling of aldimines and benzyl ethers

It was proposed that upon excitation of the  $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$  photocatalyst, PCET oxidation of methyl thioglycolate **623**, facilitated by LiOAc, yields the thiyl radical **624**. Hydrogen-atom abstraction from the benzyl ether affords the benzylic ether radical **625**, which undergoes C–C bond formation with the  $\alpha$ -amino anion radical generated via single electron reduction of the aldimine, thus closing the photocatalytic cycle and furnishing the  $\beta$ -amino ether product **622**. Although not mentioned by the authors, the substantial difference in reduction potential between the reduced  $\text{Ir}^{\text{II}}$  species ( $E_{1/2}^{\text{III/II}} = -1.51$  V vs. SCE) and *N*-benzylideneaniline ( $E_{1/2}^{\text{red}} = -1.91$  V vs. SCE) renders this SET extremely endergonic; therefore, PCET directly forming the  $\alpha$ -amino radical **626** would appear more likely. Importantly, good yields were obtained with electron-rich and electron-deficient, as well as heteroaromatic substituents. In 2015, Macmillan reported the similar coupling of aldimine-derived  $\alpha$ -amino radicals with  $\beta$ -enaminyll radicals to form  $\gamma$ -aminoketones in good yields<sup>556</sup>. The

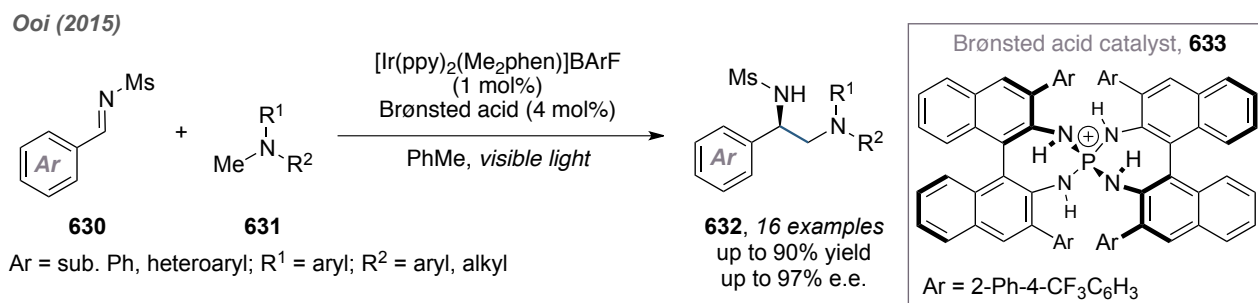
addition of DABCO was crucial as a redox mediator between the  $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$  photocatalyst and electron-rich enamine.

At the same time, Rueping disclosed a photocatalytic imino-pinacol coupling using aryl-derived aldimines **627** in moderate to good yields (Scheme 153)<sup>557</sup>. Using an  $[\text{Ir}\{\text{F}(\text{CF}_3)\text{ppy}\}_2(\text{bpy})]\text{PF}_6$  photocatalyst, the authors propose that reductive quenching of the photocatalyst using  $\text{Bu}_3\text{N}$  affords the Lewis acidic radical cation that engages the basic iminium ion through a two-centre/three-electron bond **629**, lowering the barrier for SET. Subsequent single electron reduction and homocoupling of the  $\alpha$ -amino anion radical forms the desired product **628** upon protonation.



**Scheme 153** | Photoredox catalyzed imino-pinacol coupling of aryl aldimines

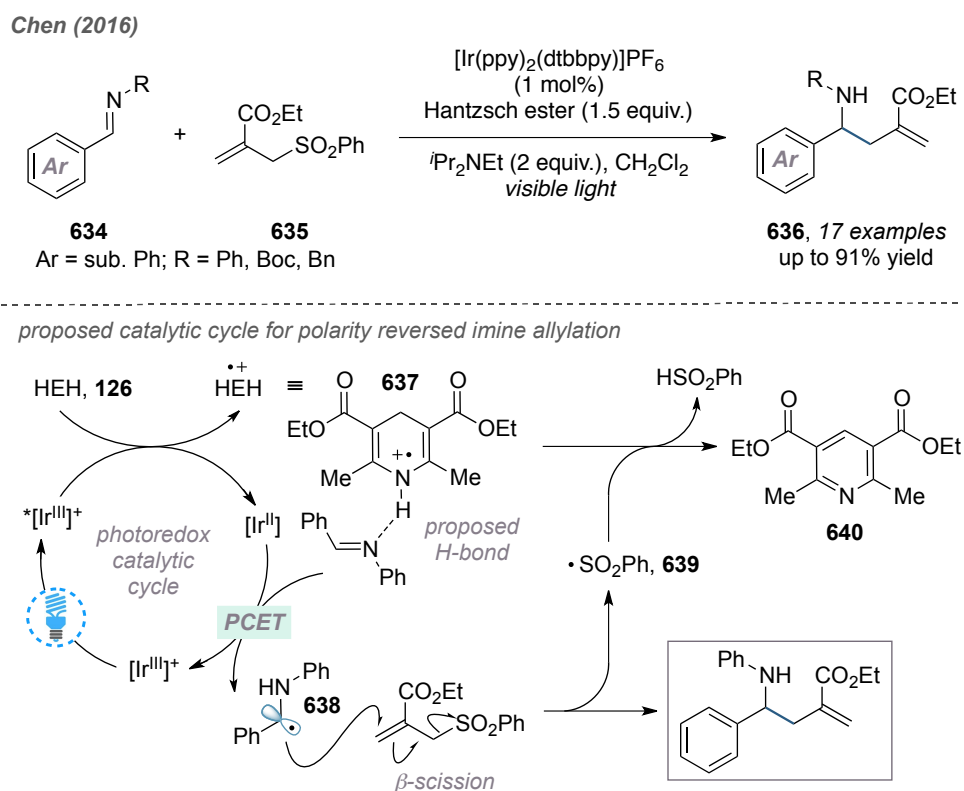
In 2015, Ooi reported an elegant dual photoredox/chiral Brønsted acid catalyzed coupling of *N*-sulfonyl aldimines **630** and *N*-methyl anilines **631** in good yields and enantioselectivities (up to 90% yield, up to 97% e.e.) (Scheme 154)<sup>393</sup>. The authors propose that upon excitation of the  $[\text{Ir}(\text{ppy})_2(\text{Me}_2\text{phen})]\text{BARF}$  photocatalyst with visible light, reductive quenching of the *N*-methyl aniline leads to the  $\alpha$ -amino radical upon deprotonation of the radical cation. Subsequently, single electron reduction of the *N*-sulfonyl aldimine affords the  $\alpha$ -amino anion radical that forms a chiral ion pair with a catalytic *P*-spiro tetraaminophosphonium cation **633**. Radical-radical coupling occurs asymmetrically to afford the 1,2-diamine product **632**. In 2016, Rueping described a conceptually similar achiral version of the reaction using aryl aldimines<sup>558</sup>.



**Scheme 154** | Dual photoredox/chiral Brønsted acid catalyzed coupling of *N*-sulfonyl aldimines and *N*-methyl anilines

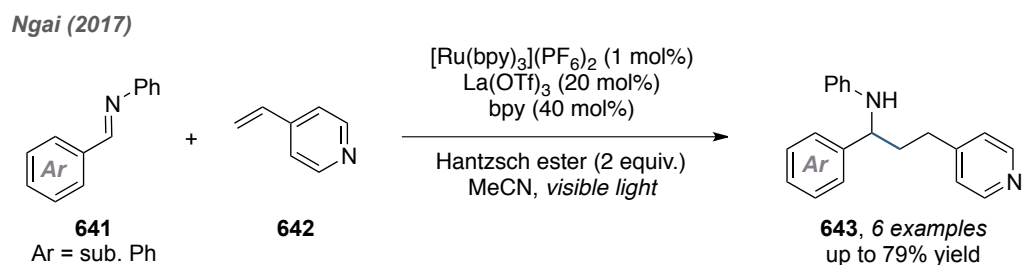
Another important class of transformation is the addition of  $\alpha$ -amino radicals to activated electrophilic alkenes. In 2016, Chen described the photocatalytic allylation and Michael addition of

*N*-benzylideneanilines **634** with Hantzsch ester **126** as a stoichiometric reductant in moderate to good yields (Scheme 155)<sup>559</sup>. Impressively, the authors reported that the allylation also works for a small number of alkylideneanilines; reductive quenching of the Ir<sup>III</sup>-photocatalyst by Hantzsch ester leads to HEH<sup>•+</sup> **637**, which activates these more challenging imines towards PCET forming the  $\alpha$ -amino radical **638**. Due to the high reactivity of  $\alpha$ -ester radicals towards oligomerization after Giese-type additions, the authors used allyl sulfones **635** that undergo  $\beta$ -scission with loss of the sulfonyl radical **639**, constituting a useful polarity reversed (umpolung) approach to the allylation of imines (**636**). A similar reaction was later published by Dixon using Eosin Y as an organic photocatalyst<sup>560</sup>.



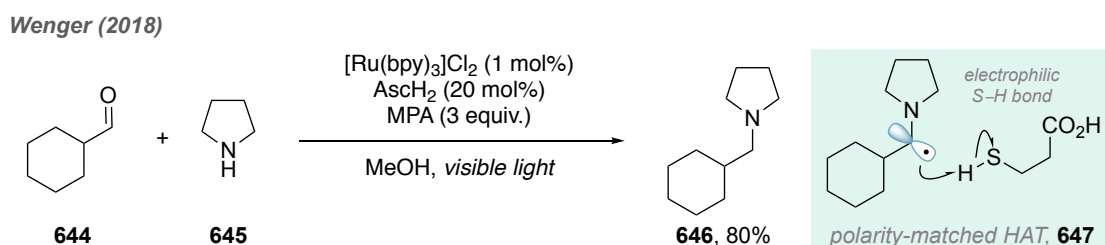
**Scheme 155** | Photoredox catalyzed polarity reversed aldimine allylation

Recently, Ngai detailed the dual photoredox/Lewis acid catalyzed reductive coupling of *N*-benzylideneanilines **641** and vinyl pyridines **642** in good yields (Scheme 156)<sup>561</sup>. Usefully, this process offers a complementary approach to that of Krische whereby C–C coupling occurs at the  $\alpha$ -position to the vinyl moiety (Scheme 35)<sup>184</sup>. By employing the catalytically generated HEH<sup>•+</sup> **637** to quench the Ru<sup>II</sup>-photocatalyst, the resulting pyridinium ion is able to activate the imine towards PCET. The resulting  $\alpha$ -amino radical is able to add to the La(OTf)<sub>3</sub>-activated vinyl pyridine forming the stable heterobenzylic radical, which undergoes HAT from the Hantzsch ester forming the product **643** and regenerating HEH<sup>•+</sup>.



**Scheme 156** | Dual photoredox/Lewis acid catalyzed reductive coupling of benzylideneanilines and vinyl pyridines

Although recent advances have expanded the capability of photocatalytic C=N bond reductive alkylation, the scope of imines and acceptors is limited, especially when considering the paucity of studies using alkyl-derived imine precursors. Along these lines, the photocatalytic single-electron reduction of alkyl-iminium ions remains rare. While ‘all-alkyl’ substituted iminium ions possess similarly high reduction potentials to *N*-benzylideneanilines (Scheme 151), they lack the available orbitals to undergo Brønsted or Lewis acid assisted PCET. Moreover, alkyl-substituted iminium ions exist (often unfavourably) in equilibrium with the corresponding enamines, which also undergo oxidative SET reactions, presenting competing pathways (see Scheme 160). To the best of our knowledge, Wenger described the sole photocatalytic single electron reduction of an alkyl iminium ion in 2018 (Scheme 157). Using a dual catalytic Ru<sup>II</sup>/ascorbic acid system, alongside superstoichiometric thiol reductant, cyclohexane carboxaldehyde **644** and pyrrolidine **645** underwent photocatalytic reductive amination (**646**) via polarity matched HAT **647** in 80% yield<sup>562</sup>.



**Scheme 157** | Photoredox catalyzed polarity matched reductive amination

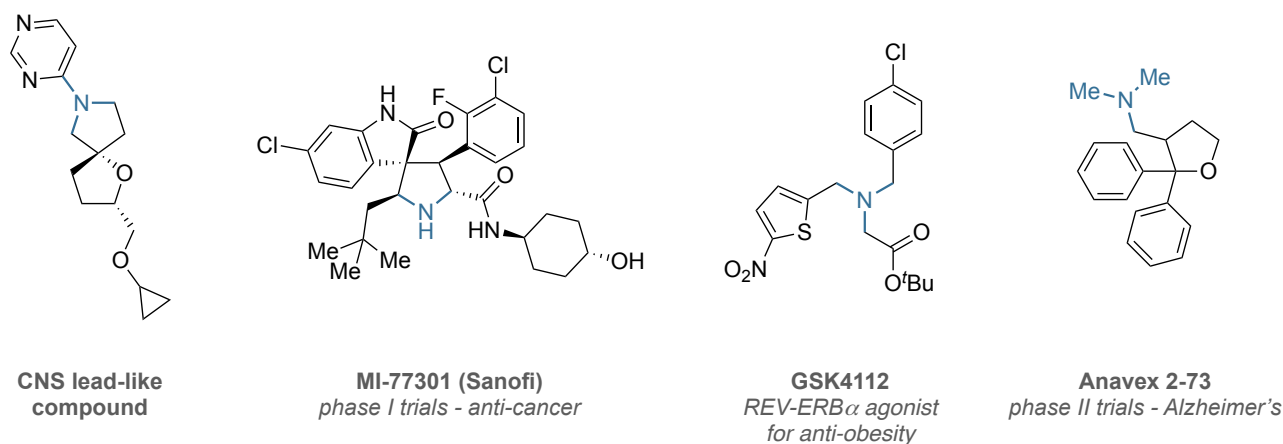
## 4.2 Project aims

In contrast to  $\alpha$ -amino radicals bearing stabilizing groups (e.g. acyl<sup>563–566</sup>, sulfonyl<sup>567</sup>), the generation of alkyl  $\alpha$ -amino radicals, and their addition to unactivated alkenes, has been traditionally low yielding. This low reactivity has been ascribed to the loss of stabilization of the radical provided by the amino group in the transition state, the nucleophilic nature of the  $\alpha$ -amino radical, and the tendency of the radical to undergo dimerization<sup>568</sup>. Strategies employing SmI<sub>2</sub> have circumvented these obstacles by further reduction of the resulting alkyl radical to the corresponding

organosamarium compound, thus driving the equilibrium towards the products<sup>569</sup>. However, despite these efforts, the use of strong stoichiometric reductants and harsh reaction conditions limits the generality of these transformations.

Inspired by the challenges imposed by these limitations, it was reasoned that a distinct photocatalytic process capable of exploiting the C–C bond forming capability of feedstock alkenes and  $\alpha$ -amino radicals, generated from the well-established union between dialkylamines and carbonyl compounds (via an iminium ion), would significantly expand the remit of complex amine synthesis. We envisioned that SET from a highly reducing photocatalyst would generate an ‘all-alkyl’  $\alpha$ -amino radical that could add to an alkene forming an alkyl radical. Subsequent polarity-matched HAT<sup>570</sup> from a suitable donor would drive the equilibrium towards the aminoalkylated product.

Based on this design plan, we aimed to devise a range of intramolecular and intermolecular multicomponent amine syntheses, accessing tertiary amine products that would be challenging and tedious to access via conventional efforts in one step. The development of a simple, practical and diverse methodology for the preparation of these important molecules would be of significant interest in drug-discovery platforms. Recently, such functionalized small-molecule amine-derived heterocycles have garnered increasing attention as lead compounds in CNS<sup>5,571,572</sup>, anti-cancer<sup>573</sup>, and anti-obesity studies<sup>574</sup> (Figure 5).

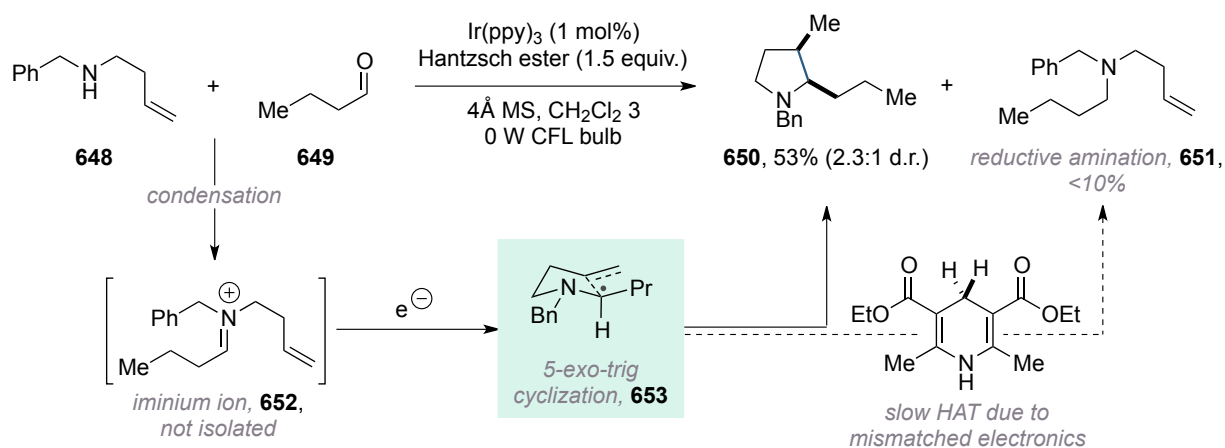


**Figure 5** | The importance of complex small molecule amines in drug-discovery platforms

### 5.3 Results and discussion

We first set about evaluating the intramolecular 5-*exo*-trig cyclization of *N*-benzylbut-3-en-1-amine **648** with butyraldehyde **649** via the single electron reduction of the iminium ion **652** to the

corresponding  $\alpha$ -amino radical **653**. An initial hit was observed using equimolar amine and aldehyde in the presence of the strongly reducing Ir(ppy)<sub>3</sub> photocatalyst (1 mol%), 4Å molecular sieves, Hantzsch ester (1.5 equiv.) and a 30 W CFL light bulb in dichloromethane (Scheme 158). Remarkably, sequential condensation, reduction, cyclization and HAT occurred to deliver the substituted pyrrolidine product **650** in 53% yield and 2.4:1 d.r. (*cis:trans* by GC-FID). Pleasingly, the crude reaction profile showed only product and remaining starting material with <10% tertiary amine product **651** resulting from reductive amination. In contrast to the photocatalytic reductive amination protocol reported by Wenger (Scheme 157)<sup>562</sup>, the more electron-rich Hantzsch ester appears to engage in a polarity-matched HAT, selectively reacting with the low-concentration of primary alkyl-radical over the nucleophilic  $\alpha$ -amino radical intermediate **653** (Scheme 158). The diastereoselectivity was consistent with that of the Beckwith model for radical cyclizations (Scheme 158)<sup>575</sup>, wherein the  $\pi$ -character of the  $\alpha$ -amino radical and LUMO of the alkene subunit create a strong secondary orbital interaction at the *cis*-saddle points<sup>576,577</sup>.



**Scheme 158** | Photoredox catalyzed reductive cyclization of *N*-benzylbut-3-en-1-amine with butyraldehyde

With this promising result in hand we turned our attention to optimizing the intramolecular cyclization. Importantly, upon subjecting the corresponding tertiary amine **651** to the reaction conditions, none of the pyrrolidine product was formed, discounting a potential stepwise *in-situ* reductive amination and oxidative cyclization mechanism. Furthermore, no reaction was observed in the absence of photocatalyst or when conducted in the dark (Table 16, entries 2 and 3). Interestingly, 16% of the cyclized product **650** was observed in the absence of Hantzsch ester **126**, presumably resulting from non-selective HAT from the reactive primary radical (Table 16, entry 4). Moreover, both increasing and reducing the loading of Hantzsch ester **126** to one and two equivalents led to a drop in yield to 39% and 46% respectively (Table 16, entries 5 and 6). *N*-benzyl-1,4-dihydronicotinamide (BnNADH), a biomimetic Hantzsch ester, afforded the desired pyrrolidine **650** in trace yield (Table 16, entry 7). Neither increasing the quantity of molecular sieves nor doubling

the loading of Ir(ppy)<sub>3</sub> had appreciable effect on the yield (Table 16, entries 8 and 9). Additionally, the reaction was tolerant of trace oxygen – affording the desired product **650** in 53% yield without degassing of solvent (Table 16, entry 10).

Entry	Conditions	Yield (%) <sup>a</sup>	Entry	Conditions	Yield (%) <sup>a</sup>
1	standard	53	6	HEH (2 equiv.)	46
2	no Ir(ppy) <sub>3</sub>	trace	7	BnNADH	trace
3	dark	0	8	4 Å MS (twice loading)	48
4	no HEH	16	9	Ir(ppy) <sub>3</sub> (2 mol%)	54
5	HEH (1 equiv.)	39	10	not degassed	53

**Table 16** | Evaluation of reaction conditions for the reductive cyclization of *N*-benzylbut-3-en-1-amine with butyraldehyde. <sup>a</sup>Yields determined by GC-FID against internal standard *n*-dodecane.

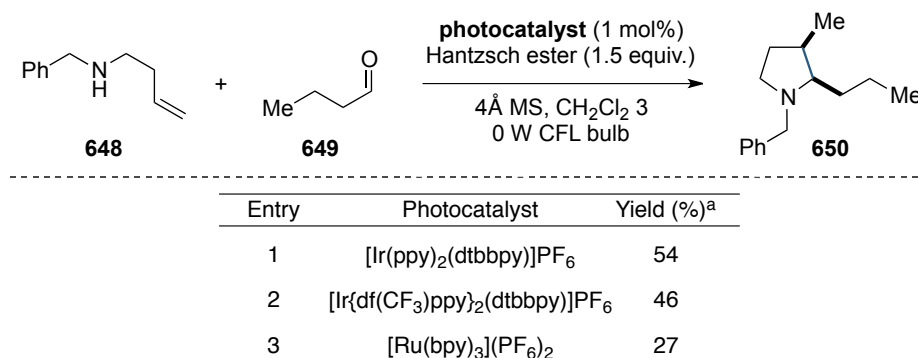
We next sought to identify whether changing the solvent had a positive effect on the yield. Disappointingly, more polar solvents MeOH, DMF and DMPU, which can better stabilize the charged iminium ion **652**, afforded the cyclized product **650** in less than 10% yield (Table 17, entries 1–3). Similarly, MeCN and PhCF<sub>3</sub> afforded the product **650** in diminished 31% and 15% yield respectively (Table 17, entries 4 and 5).

Entry	Solvent	Yield (%) <sup>a</sup>			
1	MeOH	<10			
2	DMF	<10			
3	DMPU	0			
4	MeCN	31			
5	PhCF <sub>3</sub>	15			

**Table 17** | Evaluation of reaction solvents for the reductive cyclization of *N*-benzylbut-3-en-1-amine with butyraldehyde. <sup>a</sup>Yields determined by GC-FID against internal standard *n*-dodecane.

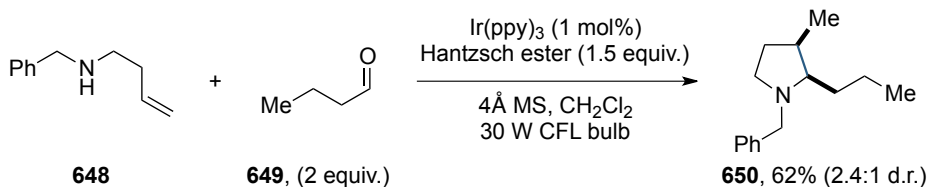
Finally, we turned our attention to alternative photocatalysts. Both [Ir(ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub> and [Ir{dF(CF<sub>3</sub>)ppy}<sub>2</sub>(bpy)]PF<sub>6</sub> afforded the desired pyrrolidine **650** in good yields (54% and 46%) (Table 18, entries 1 and 2); however, [Ru(bpy)<sub>3</sub>](PF<sub>6</sub>)<sub>2</sub> furnished the product **650** in a lower 27% yield, despite having a similar reduction potential to [Ir{dF(CF<sub>3</sub>)ppy}<sub>2</sub>(bpy)]PF<sub>6</sub> (Table 18, entry 3).





**Table 18** | Evaluation of photocatalysts for the reductive cyclization of *N*-benzylbut-3-en-1-amine with butyraldehyde.  
<sup>a</sup>Yields determined by GC-FID against internal standard *n*-dodecane.

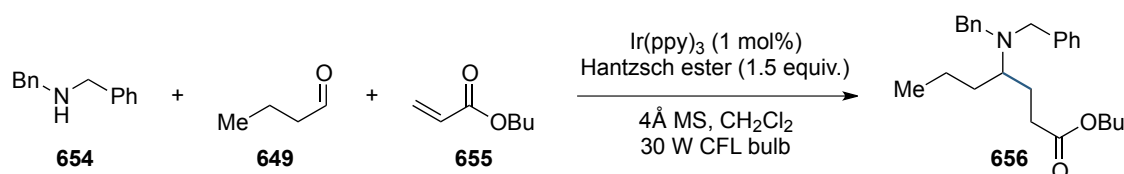
Gratifyingly, upon doubling the equivalents of butyraldehyde **649**, the yield of pyrrolidine **650** increased to a moderate 62% yield (Scheme 159). Currently, N. J. Flodén and Dr D. Willcox are pursuing further studies on the intramolecular cyclization of  $\alpha$ -amino radicals onto unactivated alkenes.



**Scheme 159** | Reaction conditions for the reductive cyclization of *N*-benzylbut-3-en-1-amine with butyraldehyde

Having established the capability of alkyl iminium ions to undergo single electron reduction to the corresponding  $\alpha$ -amino radical, we turned our attention towards the intermolecular three component coupling of aldehyde, secondary amine and alkene for the synthesis of complex tertiary amines. While the photocatalytic oxidative generation of  $\alpha$ -amino radicals and their addition to activated alkenes has been well established, the corresponding reductive process has been plagued with issues of poor reactivity (*vide supra*). However, given the efficacy of Hantzsch ester **126** in selective HAT for the intramolecular cyclization of  $\alpha$ -amino radicals, we examined the reaction between dibenzylamine **654** (chosen for its synthetic versatility), butyraldehyde **649** (1 equiv.), and *n*-butyl acrylate **655** (1.5 equiv.) with Hantzsch ester **126** (1.5 equiv.), 4 Å molecular sieves, and Ir(ppy)<sub>3</sub> photocatalyst (1 mol%) in dichloromethane, irradiated by a 30 W CFL light bulb. The desired tertiary amine product **656** was furnished in a 20% yield (Table 19, entry 1). In line with previous findings, increasing the equivalents of butyraldehyde **649** from 1 to 1.5 equivalents resulted in a substantial increase in the yield to 42% (Table 19, entry 2). Moreover, increasing both the equivalents of butyraldehyde **649** and *n*-butyl acrylate **655** to 2 equivalents resulted in a further increase to 58% yield (Table 19, entry 3). Unfortunately, further increasing the equivalents of *n*-butyl acrylate to 2.5 equivalents resulted in a diminished 47% yield of the product **656** (Table 19, entry 4).

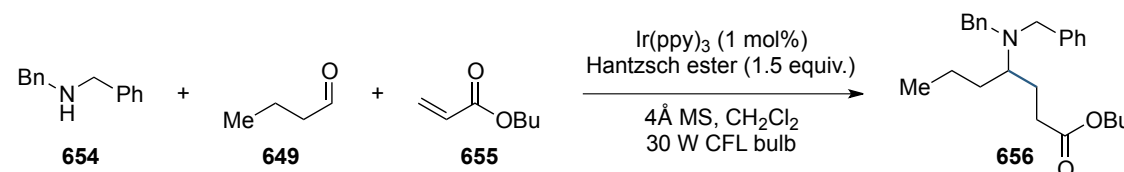




Entry	649 (equiv.)	655 (equiv.)	Yield (%) <sup>a</sup>
1	1	1.5	20
2	1.5	1.5	42
3	2	2	58
4	2	2.5	47

**Table 19** | Evaluation of reaction stoichiometry for the photoredox catalyzed multicomponent synthesis of tertiary alkylamines. <sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane.

Importantly, no reaction was observed in the absence of light or photocatalyst (Table 20, entries 1 and 2), however more prominently, no reaction was observed in the absence of Hantzsch ester **126** (Table 20, entry 3) – perhaps highlighting its significance in the polarity matched HAT. The photocatalyst [Ir(ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub>, which behaved similarly to Ir(ppy)<sub>3</sub> for the intramolecular cyclization, afforded the tertiary amine product **656** in a lower 49% yield (Table 20, entry 4). Furthermore, the addition of catalytic acid AcOH (20 mol%) resulted in a significant decrease in the yield of the product **656** to 19% (Table 20, entry 5).



Entry	Conditions	Yield (%) <sup>a</sup>
1	no Ir(ppy) <sub>3</sub>	0
2	dark	0
3	no HEH	0
4	[Ir(ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	49
5	AcOH (20 mol%)	19

**Table 20** | Evaluation of reaction conditions for the photoredox catalyzed multicomponent synthesis of tertiary alkylamines. <sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane.

At this time, D. Reich joined the project in order to help optimize the multicomponent photocatalytic synthesis of tertiary alkylamines. Immediately, it was discovered that changing the reaction vessel from a microwave tube (10 mL) to a smaller scintillation vial (4 mL) increased the yield to 66% (Table 21, entry 1). Critically, the principle differences between the two vessels are the smaller wall-thickness and larger exposed surface area of the reaction medium. The Beer–Lambert law states that photonic flux decreases exponentially with increasing depth in the reaction medium. Therefore, it is reasonable to assume that only the media close to the vessel wall will experience irradiation<sup>578</sup>, this

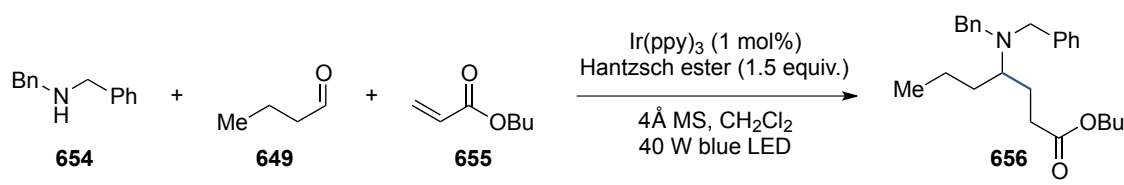
problem is further compounded by the heterogeneous nature of the reaction<sup>579</sup>. As such, the reaction is likely to be “photon-limited” by virtue of the low photon penetration due to poor surface area exposure<sup>580</sup>. Given that an increase in light intensity is directly proportional to the concentration of excited photocatalyst, and hence reaction efficiency, we turned our attention towards optimizing the physical setup.

Remarkably, D. Reich found that upon changing from a 30 W CFL bulb to a directed 40 W blue LED lamp (Kessil A160WE), the yield increased to 99% (Table 21, entry 2). Importantly, the narrow wavelength band emitted by the 40 W blue LED lamp ( $\lambda \approx 400 - 500$  nm,  $\lambda_{\text{max}} = 462$  nm; see Appendix II, figure 10) has good overlap with the <sup>3</sup>MLCT range of the Ir(ppy)<sub>3</sub> photocatalyst ( $\lambda \approx 430 - 500$  nm)<sup>581</sup>. Moreover, upon reducing the equivalents to 1:1.1:1.1 (**654/649/655**), no change to the yield of the amine product **656** was observed (Table 21, entry 3). In fact, upon reducing the reaction time to 2 hours, the tertiary amine product **656** was furnished in 98% yield (Table 21, entry 4).

<b>654</b>	<b>649</b>	<b>655</b>															
<table border="1"> <thead> <tr> <th>Entry</th><th>Conditions</th><th>Yield (%)<sup>a</sup></th></tr> </thead> <tbody> <tr> <td>1<sup>o</sup></td><td>scintillation vial (4 mL)</td><td>66</td></tr> <tr> <td>2<sup>o</sup></td><td>40 W Kessil A160WE</td><td>99</td></tr> <tr> <td>3<sup>o</sup></td><td>Kessil, (<b>649:655</b> = 1.1:1.1), 16 h</td><td>99</td></tr> <tr> <td>4</td><td>Kessil, (<b>649:655</b> = 1.1:1.1), 2 h</td><td>98</td></tr> </tbody> </table>			Entry	Conditions	Yield (%) <sup>a</sup>	1 <sup>o</sup>	scintillation vial (4 mL)	66	2 <sup>o</sup>	40 W Kessil A160WE	99	3 <sup>o</sup>	Kessil, ( <b>649:655</b> = 1.1:1.1), 16 h	99	4	Kessil, ( <b>649:655</b> = 1.1:1.1), 2 h	98
Entry	Conditions	Yield (%) <sup>a</sup>															
1 <sup>o</sup>	scintillation vial (4 mL)	66															
2 <sup>o</sup>	40 W Kessil A160WE	99															
3 <sup>o</sup>	Kessil, ( <b>649:655</b> = 1.1:1.1), 16 h	99															
4	Kessil, ( <b>649:655</b> = 1.1:1.1), 2 h	98															

**Table 21** | Evaluation of reaction parameters for the photoredox catalyzed multicomponent synthesis of tertiary alkylamines. <sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane. <sup>o</sup>Reaction conducted by D. Reich

Interestingly, D. Reich found that upon conducting the reaction with freshly distilled aldehyde **649**, no product **656** was obtained (Table 22, entry 1). This result led us to deduce that trace butyric acid in the butyraldehyde **649** was likely catalyzing the formation of the iminium ion **657**. Accordingly, upon using freshly distilled butyraldehyde, with the addition of butyric acid as an additive (10 mol%), the tertiary amine **656** was delivered in 97% yield (Table 22, entry 2). Upon switching to propionic acid (10 mol%), the desired product **656** was obtained in near quantitative yield (Table 22, entry 3).

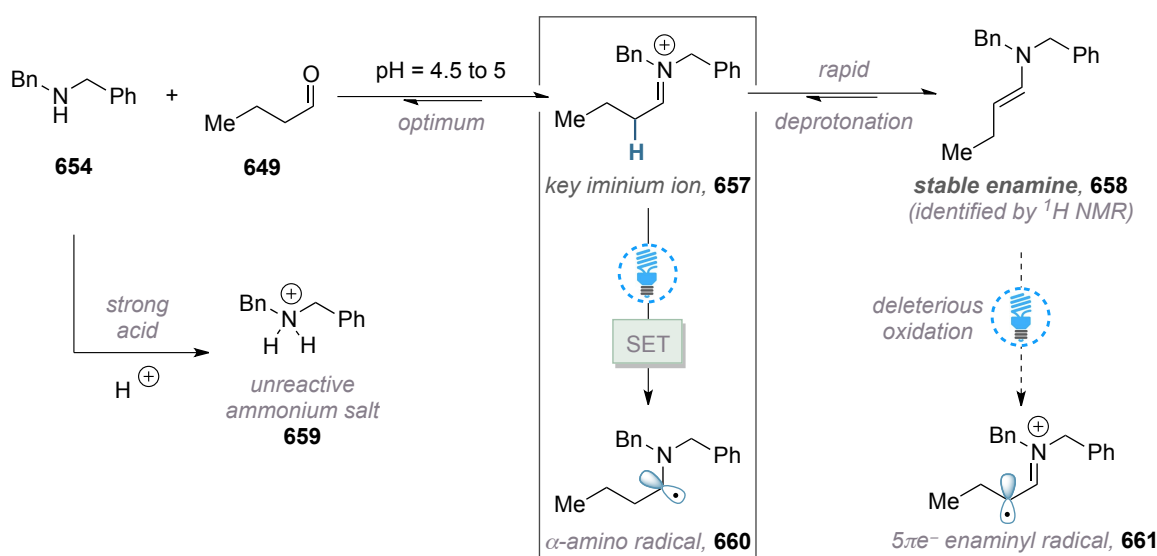


Entry	Conditions	Yield (%) <sup>a</sup>
1 <sup>◊</sup>	freshly dist. PrCO <sub>2</sub> H	0
2 <sup>◊</sup>	PrCO <sub>2</sub> H (10 mol%)	97
3	EtCO <sub>2</sub> H (10 mol%)	99

**Table 22** | Evaluation of acid additives for the photoredox catalyzed multicomponent synthesis of tertiary alkylamines.

<sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane. <sup>◊</sup>Reaction conducted by D. Reich

The rate of condensation between amines (**654**) and aldehydes (**649**) has been shown to be highly dependent upon pH, wherein decreasing pH has been shown to be beneficial (Scheme 160)<sup>582</sup>. However, the reaction rate is severely diminished under acidic conditions due to protonation of the amine (**659**). On the other hand, formation of the key iminium ion **657** can only be achieved under strongly acidic conditions due to competing base-induced tautomerization to the unreactive enamine **658**. Problematically, the electron-rich enamine can undergo facile deleterious oxidation to the corresponding  $5\pi e^-$  enaminyll radical **661** (Scheme 160)<sup>583</sup>. In addition, the nature of the ion-pairing of the iminium ion and the conjugate base of the acid catalyst is likely to effect the solubility and reactivity of the system<sup>584,585</sup>. Therefore, in order to understand the predominant species in the reaction medium, the individual components were combined and analyzed by <sup>1</sup>H NMR (*see* Appendix II, figure 11). The corresponding enamine **658** was present in quantitative yield, which we conclude is an off-cycle intermediate that provides a stable precursor to the reactive iminium ion **657** upon protonation (Scheme 160).



**Scheme 160** | Role of acid catalysis in the photoredox catalyzed reduction of alkyl iminium ions

To this end, D. Reich conducted a screen of acid catalysts on a more sterically demanding system utilizing dibenzylamine **654** and cyclohexane carboxaldehyde **644**, wherein condensation is likely to be slow. In line with earlier findings using acetic acid (Table 20, entry 5), employing stronger acids TFA [ $pK_a = 0.2^{586}$ ] and CSA [ $pK_a = 1.2^{587}$ ] resulted in moderate yield of the tertiary amine product **662** to 47% and 43% yield respectively (Table 23, entries 1 and 2). However, upon switching to catalytic propionic acid (10 mol%) [ $pK_a = 4.9^{586}$ ], the desired tertiary amine product **662** was afforded in an improved 55% yield (Table 23, entry 3). Gratifyingly, increasing the concentration of propionic acid from 10 mol% to 20 mol% resulted in an increase in yield to 66% (Table 23, entry 4); however, increasing the concentration of acid to 50 mol% and one equivalent resulted in a decrease in the yield of product **662** (Table 23, entries 5 and 6). The addition of weaker acids PPTS [ $pK_a = 5.2^{586}$ ] and HFIP [ $pK_a = 9.3^{586}$ ] also resulted in diminished efficiency, furnishing the desired tertiary amine **662** in 53% and 36% yield respectively (Table 23, entries 7 and 8). Moreover, the use of more lipophilic octanoic acid and adamantanoic acid delivered the product **662** in modest 61% and 63% yield respectively (Table 23, entries 9 and 10). Importantly, upon subjection of dibenzylamine **654**, butyraldehyde **649** and *n*-butyl acrylate **655** to the modified reaction conditions employing catalytic propionic acid (20 mol%), the desired amine **656** was generated in 98% yield (by  $^1\text{H}$  NMR) and 84% (isolated).

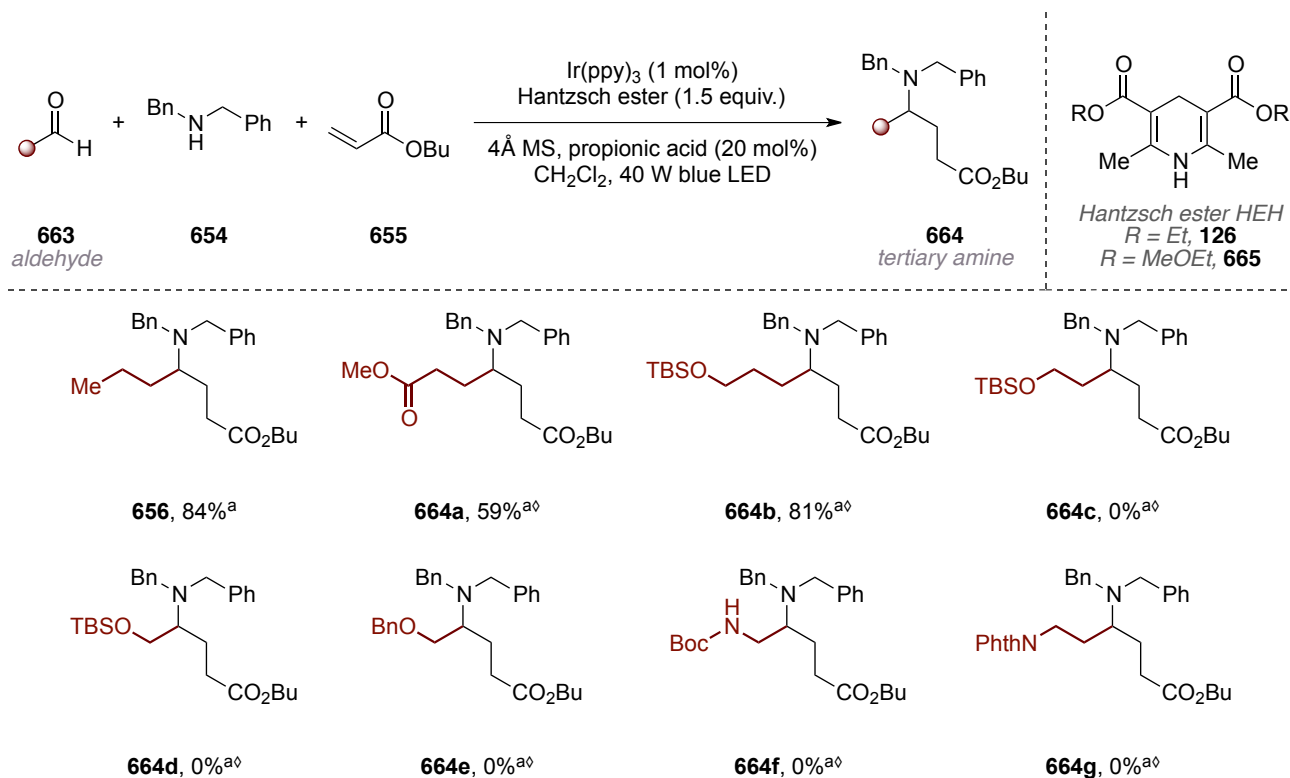
Entry	Acid (mol %)	Yield (%) <sup>a</sup>	Entry	Acid (mol %)	Yield (%) <sup>a</sup>
1 <sup>◊</sup>	TFA	47	6 <sup>◊</sup>	propionic acid (100)	57
2 <sup>◊</sup>	CSA	43	7 <sup>◊</sup>	PPTS (20)	53
3 <sup>◊</sup>	propionic acid (10)	55	8 <sup>◊</sup>	HFIP (10)	36
4 <sup>◊</sup>	propionic acid (20)	66	9 <sup>◊</sup>	octanoic acid (20)	61
5 <sup>◊</sup>	propionic acid (50)	62	10 <sup>◊</sup>	adamantanoic acid (10)	63

**Table 23** | Evaluation of acid additives for the photoredox catalyzed multicomponent synthesis of tertiary alkylamines.

<sup>a</sup>Yields determined by  $^1\text{H}$  NMR against internal standard 1,1,2,2-tetrachloroethane. <sup>◊</sup>Reaction conducted by D. Reich

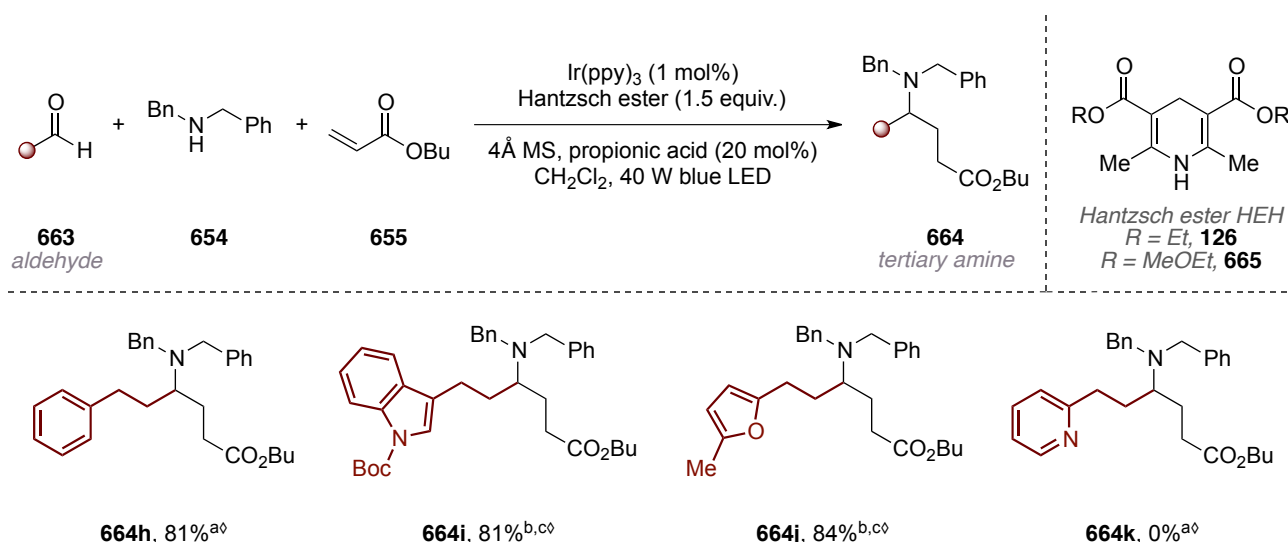
Having established optimum conditions we turned our attention to the generality of the reaction. Given the multicomponent nature of the process, we sought to undertake the substrate scope by varying one coupling partner at a time, starting with the aldehyde (Scheme 161). D. Reich found that a wide range of functionally diverse aldehydes **663** could be accommodated, including methyl 4-oxobutanoate **663a** and TBDMS-protected 4-hydroxybutyraldehyde **663b**, delivering the corresponding amino ester and amino alcohol **664a** and **664b** in 59% and 81% yield respectively.

The corresponding protected 3-hydroxypropionaldehyde and hydroxyacetaldehyde substrates **663c** and **663d** were unsuccessful under the reaction conditions, the latter presumably due to the increased acidity of the  $\alpha$ -protons of the iminium ion resulting in a higher concentration of unreactive enamine<sup>588</sup>. Similarly, *N*-Boc-aminoacetaldehyde **663f** and 3-phthalimidopropionaldehyde **664g** afforded none of the desired products.



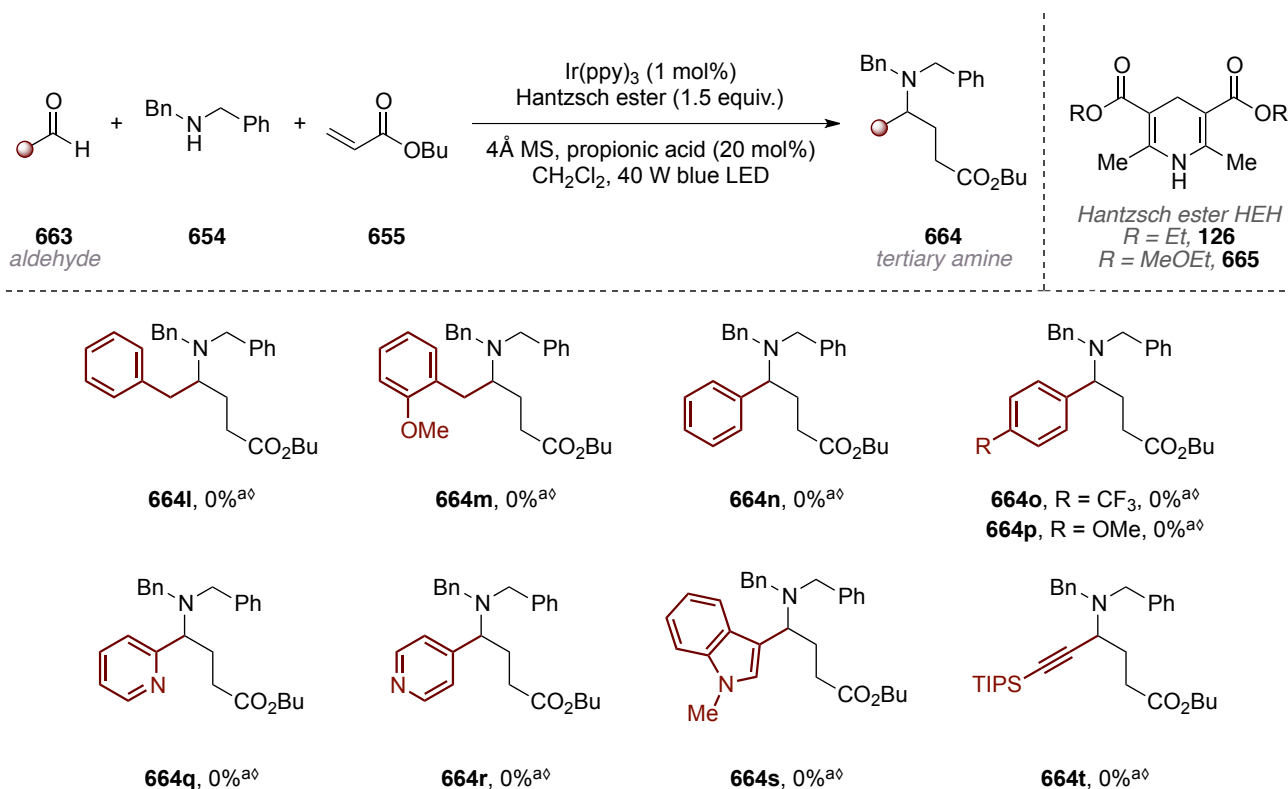
**Scheme 161** | Aldehyde substrate scope for photocatalytic multicomponent synthesis of alkyl tertiary amines. Reactions conducted using Et-HEH unless otherwise stated. <sup>a</sup>Reaction conducted using amine:aldehyde:acceptor (1:1:1.1 equivalents). <sup>†</sup>Reaction conducted by D. Reich

In addition, 3-arylpropionaldehyde scaffolds proved particularly effective under the reaction conditions, tolerating simple hydrocinnamaldehyde **663h** in 81% yield (**664h**) as well as oxidatively sensitive indole and furan moieties in an impressive 81% and 84% yield respectively (**664i** and **664j**), albeit with two equivalents of aldehyde and alkene (Scheme 162). The corresponding 3-(2-pyridyl)propionaldehyde **663k** did not afford any of the desired amine product **664k**, presumably due to its instability towards self-aldolization<sup>589</sup>. Problematically, the oxidized Hantzsch pyridine **640** severely hampered purification efforts; therefore, the more polar bis(2-methoxyethyl) Hantzsch ester (MeOEt-HEH) **665** was employed without loss in yield.



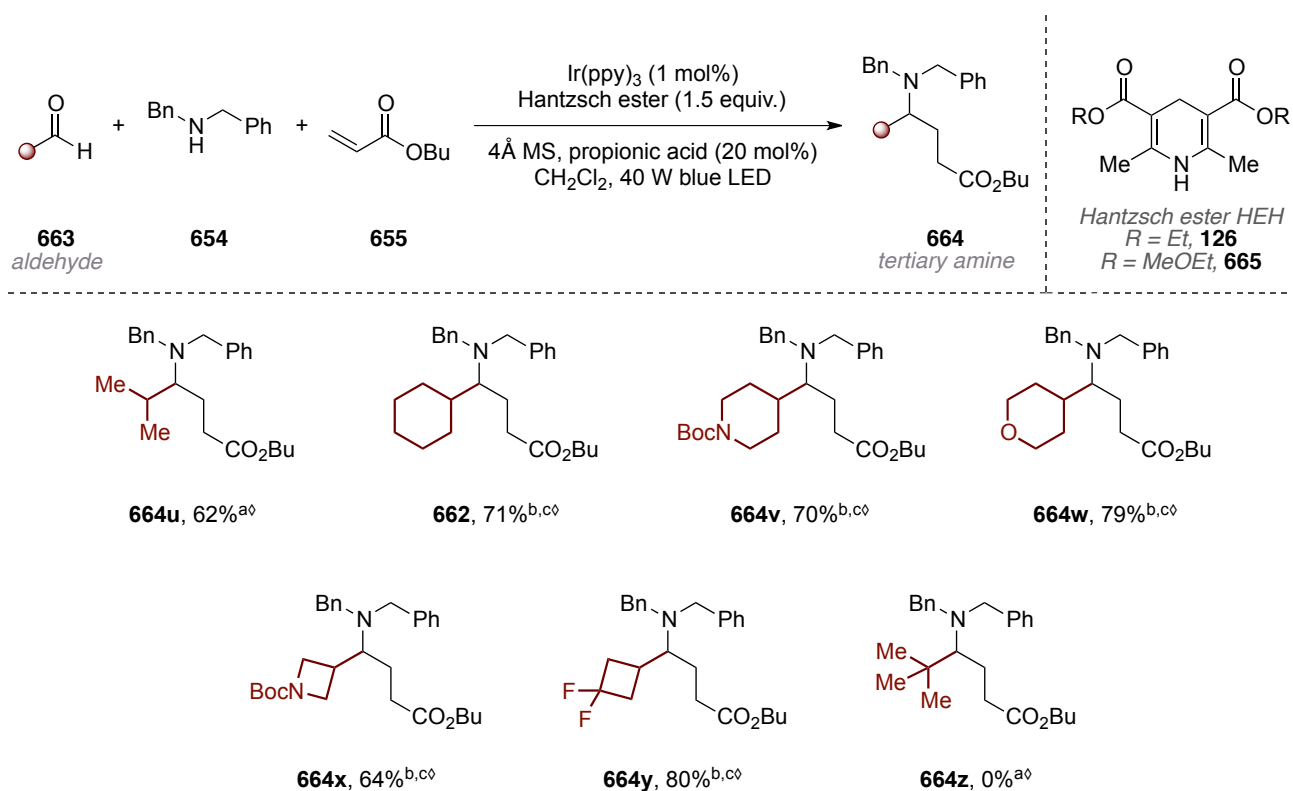
**Scheme 162** | Aldehyde substrate scope for photocatalytic multicomponent synthesis of alkyl tertiary amines. Reactions conducted using Et-HEH unless otherwise stated. <sup>a</sup>Reaction conducted using amine:aldehyde:acceptor (1:1.1:1.1 equivalents). <sup>b</sup>Reaction conducted using amine:aldehyde:acceptor (1:2:2 equivalents). <sup>c</sup>Reaction conducted using MeOEt-HEH. <sup>d</sup>Reaction conducted by D. Reich

Upon switching from hydrocinnamaldehyde **663h** to phenylacetaldehyde **663l** and **663m**, D. Reich found that the reaction failed to deliver any of the desired tertiary amine product **664l** and **664m**, arguably due to the high stability afforded to the corresponding enamine<sup>590</sup> combined with the potential for single electron oxidation (Scheme 163)<sup>591</sup>. Contrary to existing protocols for the single electron reduction of imines, benzaldehyde-derived iminium ions proved ineffectual under the reaction conditions. Although the reason is unknown, given that the addition of  $\alpha$ -amino radicals to alkenes has been shown to be reversible (*vide supra*), the highly-stabilized and more electron-deficient  $\alpha$ -aminobenzyl radical may react slowly with the electron-deficient acrylate. Unfortunately, electron-rich, electron-deficient and heteroaromatic aldehydes **663n–663s** were all rendered ineffective. Similarly, (trimethylsilyl)propiolaldehyde **663t** also proved unfruitful under the reaction conditions.



**Scheme 163** | Aldehyde substrate scope for photocatalytic multicomponent synthesis of alkyl tertiary amines. Reactions conducted using Et-HEH unless otherwise stated. <sup>a</sup>Reaction conducted using amine:aldehyde:acceptor (1:1.1:1.1 equivalents). <sup>°</sup>Reaction conducted by D. Reich

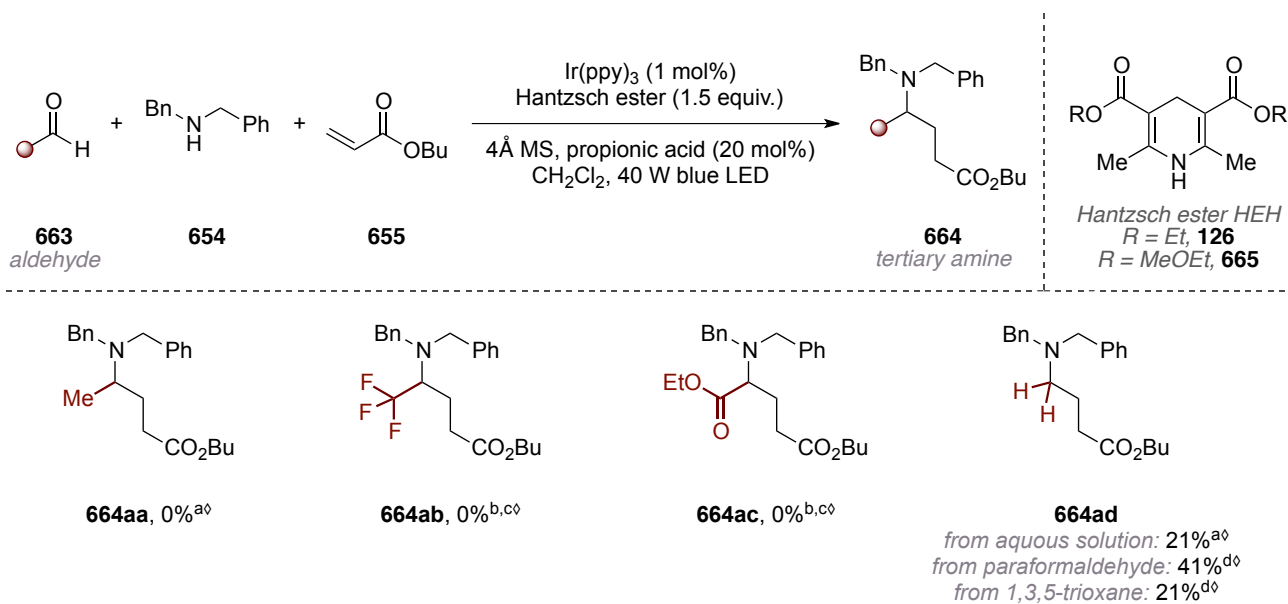
Importantly, D. Reich established that more sterically encumbered  $\alpha$ -branched aldehydes also proved capable coupling partners (Scheme 164); the coupling of isobutrylaldehyde **663u**, dibenzylamine **654** and *n*-butyl acrylate **655** furnished the corresponding tertiary amine product **664u** in a moderate 63% yield. Increasing the equivalents of aldehyde and acrylate to two facilitated the coupling between cyclohexane-, *N*-Boc-piperidine-, and tetrahydropyran carboxaldehyde **644**, **663v** and **663w** in an impressive 71%, 70% and 79% yield (**662**, **664v** and **664w**) respectively. In recent years, rigid 4-membered rings and heterocycles have attracted significant attention from the medicinal chemistry community<sup>523–526,592</sup>. Along these lines, *N*-Boc-azetidine- and 3,3-difluorocyclobutane carboxaldehyde **663x** and **663y** served as excellent substrates, delivering the tertiary amine products **664x** and **664y** in 64% and 80% yield. More hindered pivaldehyde **663z**, which cannot form an enamine, failed to deliver any of the tertiary amine product **664z**.



**Scheme 164** | Aldehyde substrate scope for photocatalytic multicomponent synthesis of alkyl tertiary amines. Reactions conducted using Et-HEH unless otherwise stated. <sup>a</sup>Reaction conducted using amine:aldehyde:acceptor (1:1.1:1.1 equivalents). <sup>b</sup>Reaction conducted using amine:aldehyde:acceptor (1:2:2 equivalents). <sup>c</sup>Reaction conducted using MeOEt-HEH. <sup>δ</sup>Reaction conducted by D. Reich

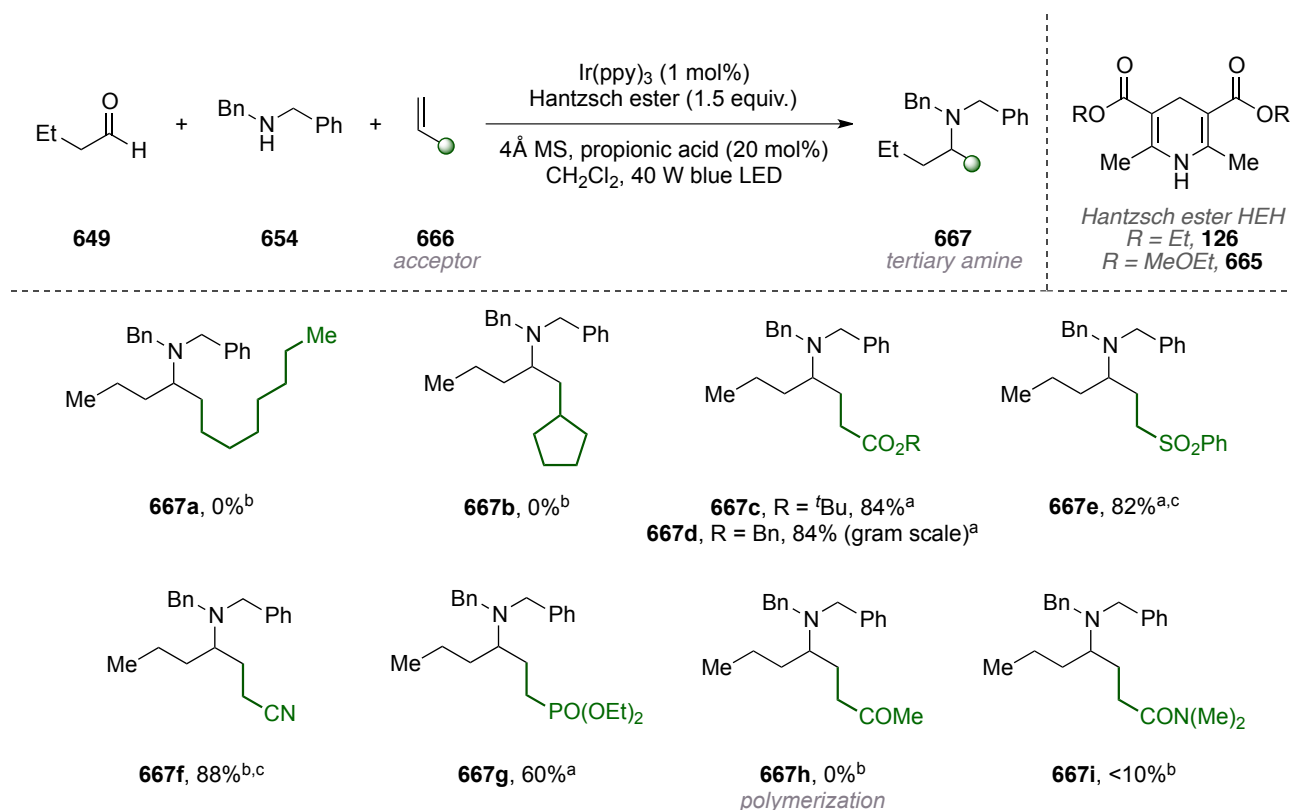
Given the clear demand for mild hydroaminomethylation strategies applicable to day-to-day synthetic chemists (Section 1.2.3), it was identified that coupling of dibenzylamine **654**, formaldehyde **663ad** and *n*-butyl acrylate **655** would constitute a valuable formal hydroaminomethylation of electron-deficient alkenes. However, we were mindful that the high reactivity of formaldehyde-derived iminium ions towards polar reduction and hydrolysis, as well as the likely polymerization of the resulting primary  $\alpha$ -amino radical, would be challenging obstacles to overcome. The similarly reactive acetaldehyde, ethyl glyoxalate and trifluoroacetaldehyde **663aa**–**663ac** all failed to deliver any of the corresponding amine products **664aa**–**664ac** (Scheme 165). Nevertheless, D. Reich found that upon treatment of formaldehyde solution (37 wt. % in water) with dibenzylamine **654** and *n*-butyl acrylate **655**, the desired  $\gamma$ -amino ester **664ad** was produced in an encouraging 21% yield. Due to the large amount of water and methanol present in formaldehyde solution, which could potentially inhibit iminium ion formation, we turned our attention towards anhydrous sources of formaldehyde. Upon switching to paraformaldehyde (3 equivalents) and pre-stirring the reaction in the dark for one hour at 45 °C, the tertiary amine product **664ad** was generated in a synthetically useful 41% yield; the corresponding cyclic trimer 1,3,5-trioxane did not afford any of the desired product.





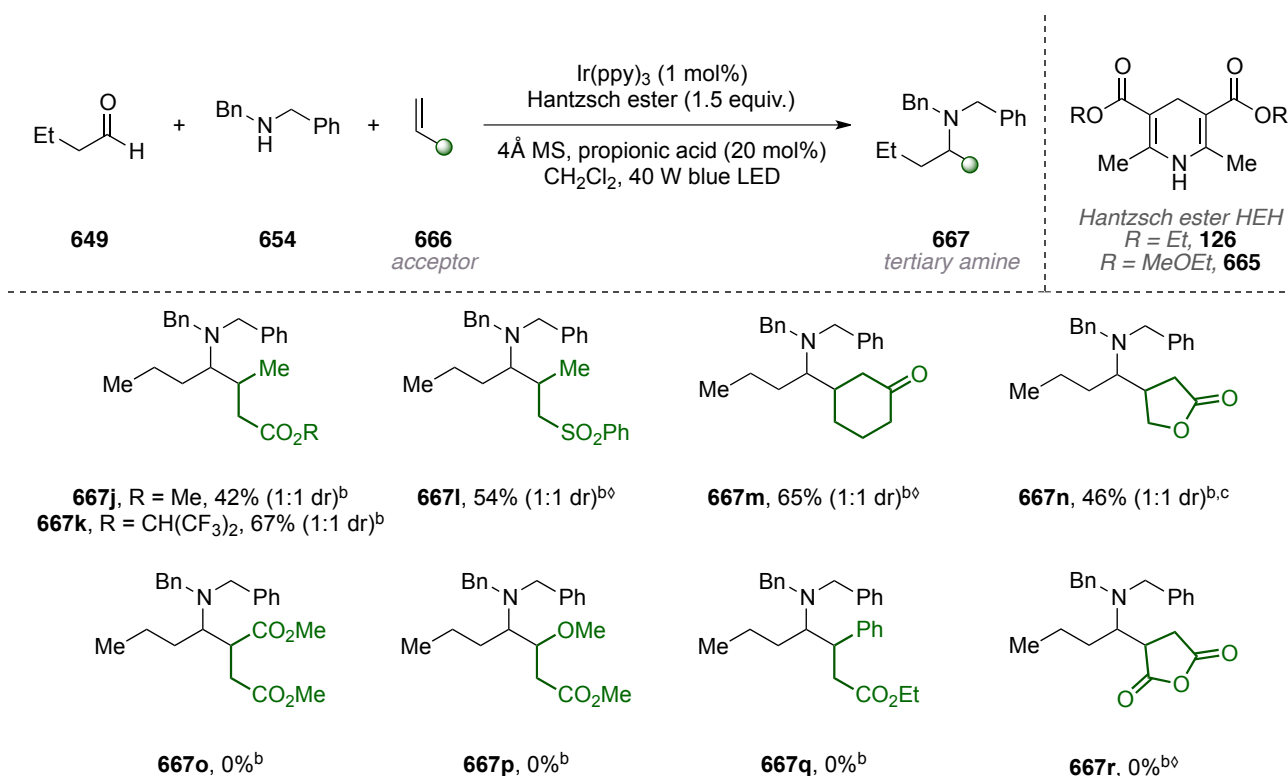
**Scheme 165** | Aldehyde substrate scope for photocatalytic multicomponent synthesis of alkyl tertiary amines. Reactions conducted using Et-HEH unless otherwise stated. <sup>a</sup>Reaction conducted using amine:aldehyde:acceptor (1:1.1:1.1 equivalents). <sup>b</sup>Reaction conducted using amine:aldehyde:acceptor (1:2:2 equivalents). <sup>c</sup>Reaction conducted using MeOEt-HEH. <sup>d</sup>Reaction mixture pre-stirred at 45 °C for 1 hour in the dark prior to irradiation <sup>‡</sup>Reaction conducted by D. Reich

Having established a clear scope of aldehydes, we turned our attention towards investigating the alkene coupling partners **666** (Scheme 166). Unsurprisingly, electron-rich aliphatic alkenes such as 1-octene **666a** and methylenecyclopentane **666b** were not compatible with the methodology, doubtless due to their poor reactivity with nucleophilic  $\alpha$ -amino radicals. However, simple acrylates bearing *tert*-butyl and benzyl ester groups **666c** and **666d** were well tolerated, both forming the tertiary amine products **667c** and **667d** in 84% yield. Importantly, the reaction could be performed on a 4 mmol scale under modified reaction conditions employing two 40 W Kessil lamps; fortuitously, the catalyst loading could be reduced to 0.5 mol% without detriment to the yield. Both vinyl sulfone **666e** and vinyl phosphonate **666g** acceptors proved competent substrates, delivering the desired products **667e** and **667g** in 82% and 60% yield respectively. Although acrylonitrile **666f** has reportedly been too unstable to act as a suitable alkene for certain radical addition reactions due to rapid polymerization<sup>593</sup>, employing two equivalents furnished the aminonitrile **667f** in an impressive 88% yield. Methyl vinyl ketone **666h** proved incompatible under the reaction conditions resulting in a complex mixture of products. Moreover, poorly electrophilic *N,N*-dimethylacrylamide **666i** afforded only trace product **667i**<sup>594</sup>.



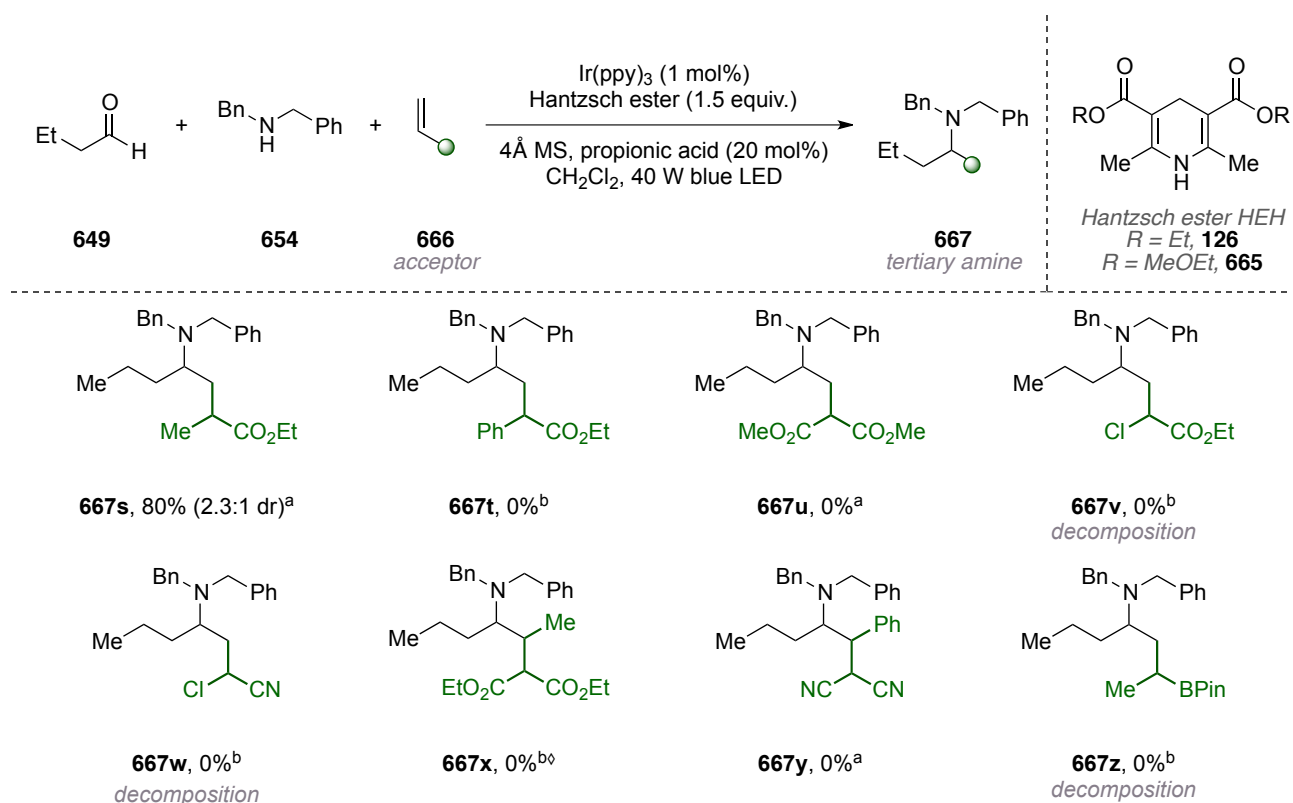
**Scheme 166** | Acceptor substrate scope for photocatalytic multicomponent synthesis of alkyl tertiary amines. Reactions conducted using Et-HEH unless otherwise stated. <sup>a</sup>Reaction conducted using amine:aldehyde:acceptor (1:1.1:1.1 equivalents). <sup>b</sup>Reaction conducted using amine:aldehyde:acceptor (1:2:2 equivalents). <sup>c</sup>Reaction conducted using MeOEt-HEH.

More hindered internal alkenes derived from crotonic acid **666j** and **666k** proved competent acceptors, affording the vicinally-substituted tertiary amine products **667j** and **667k** in moderate yields (1:1 d.r.) (Scheme 167). Moreover, propenyl sulfone **666l** served as an effective acceptor, delivering the product **667l** in 54% yield (1:1 d.r.). In addition, cyclic enones **666m** and butenolides **666n** underwent conversion to the corresponding cyclohexanone and furanone products **667m** and **667n** in 65% and 46% yield respectively (1:1 d.r.). Notably, the tolerance of a ketone moiety highlights the inherent selectivity within this iminium alkylation platform that would not be possible via other amine bond forming methodologies such as reductive amination. Internal alkenes including fumarates and cinnamates **666p–666r** proved incompatible with the reaction conditions (Scheme 167).



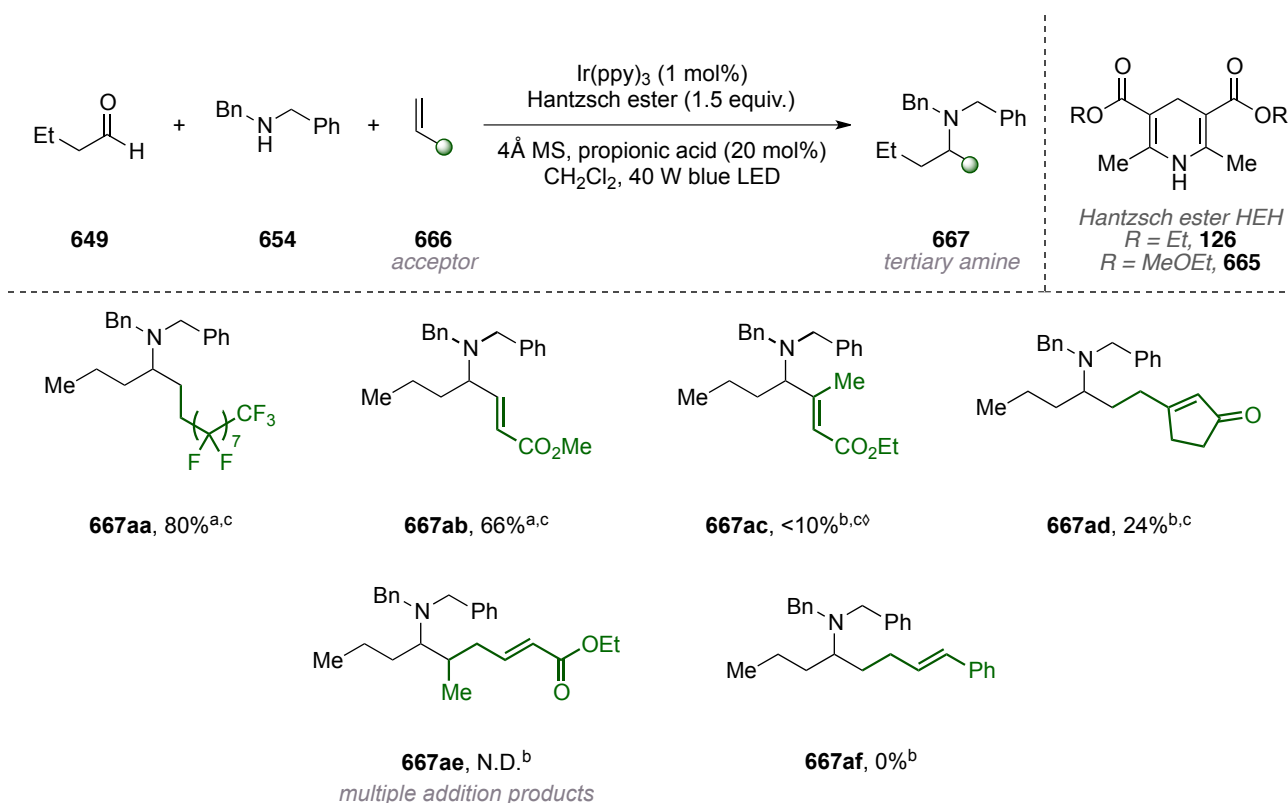
**Scheme 167** | Acceptor substrate scope for photocatalytic multicomponent synthesis of alkyl tertiary amines. Reactions conducted using Et-HEH unless otherwise stated. <sup>a</sup>Reaction conducted using amine:aldehyde:acceptor (1:1.1:1.1 equivalents). <sup>b</sup>Reaction conducted using amine:aldehyde:acceptor (1:2:2 equivalents). <sup>c</sup>Reaction conducted using MeOEt-HEH. <sup>d</sup>Reaction conducted by D. Reich

In addition to internal alkenes, poorly electrophilic 1,1-disubstituted ethyl methacrylate **666s** furnished the desired tertiary amine product **667s** in a good 80% yield with moderate diastereoselectivity (2.3:1 d.r.) (Scheme 168)<sup>594</sup>. Despite the success of this substrate, the similar ethyl atropate **666t** acceptor did not deliver any of the desired product **667t**. Moreover, highly electrophilic alkylidene malonates and malononitriles **666u–666z** proved unsuccessful –undergoing deleterious polymerization-type side reactions under the reaction conditions (Scheme 168).



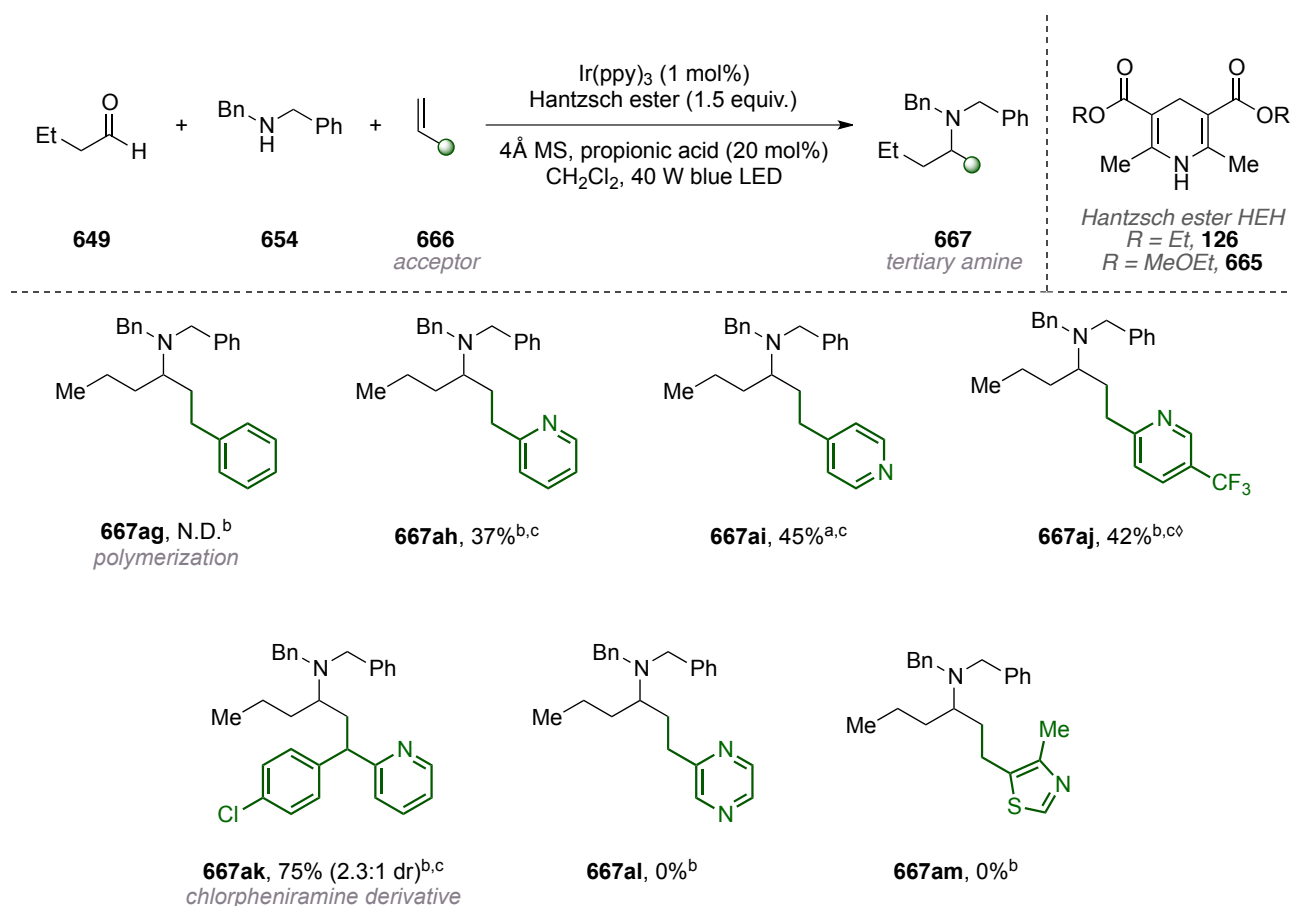
**Scheme 168** | Acceptor substrate scope for photocatalytic multicomponent synthesis of alkyl tertiary amines. Reactions conducted using Et-HEH unless otherwise stated. <sup>a</sup>Reaction conducted using amine:aldehyde:acceptor (1:1.1:1.1 equivalents). <sup>b</sup>Reaction conducted using amine:aldehyde:acceptor (1:2:2 equivalents). <sup>°</sup>Reaction conducted by D. Reich

Traditionally, the addition of  $\alpha$ -amino radicals to simple unactivated alkenes has been hampered by the poor electrophilicity of the acceptor. Therefore, we were keen to assess whether electron-deficient perfluoroalkenes would serve as radical acceptors, enabling the facile multicomponent synthesis of complex fluorinated tertiary amines. 1*H*, 1*H*, 2*H*-perfluoro-1-decene **666aa** served as an excellent coupling partner, delivering the desired product **667aa** in 80% yield (Scheme 169). Compared to alkenes, the addition of  $\alpha$ -amino radicals to alkynes has remained underexplored<sup>595</sup>. This discrepancy is surprising given the plethora of stoichiometric metal-based radical cascade reactions reported using alkynes<sup>596</sup>. Doubtless, this is due to the higher energy LUMO compared to alkenes and the late-transition state transition state involved in rehybridization<sup>597</sup>. Upon subjection of methyl propiolate **666ab** to the reaction conditions, the corresponding allylic amine **667ab** was formed in a good 66% yield, notably with exclusive (*E*)-geometry (Scheme 169). D. Reich established that ethyl 2-butynoate **666ac** gave the amine product **667ac** in diminished yield. Moreover, vinylcyclopentenone **666ad**, a 1,3-diene, proved compatible under the coupling conditions, furnishing the unsaturated amine product **667ad** in a useful 24% yield (Scheme 169). Ethyl sorbate **666ae** and phenylbutadiene **666af** did not afford any of the desired amine products.



**Scheme 169** | Acceptor substrate scope for photocatalytic multicomponent synthesis of alkyl tertiary amines. Reactions conducted using Et-HEH unless otherwise stated. <sup>a</sup>Reaction conducted using amine:aldehyde:acceptor (1:1:1:1 equivalents). <sup>b</sup>Reaction conducted using amine:aldehyde:acceptor (1:2:2 equivalents). <sup>c</sup>Reaction conducted using MeOEt-HEH. <sup>d</sup>Reaction conducted by D. Reich

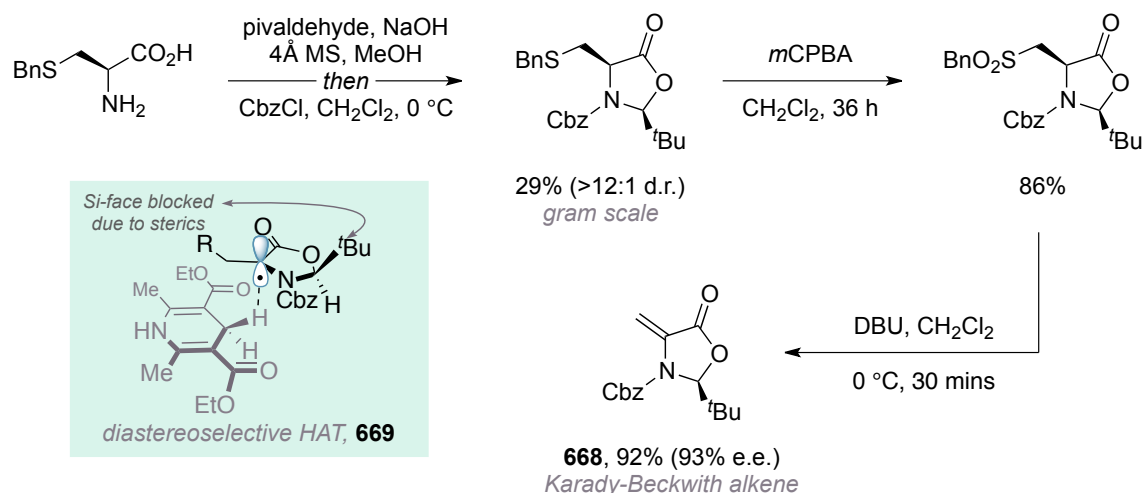
We next investigated the scope of vinyl arene acceptors (Scheme 170), given the strategic importance of the phenpropylamine scaffold in medicinal chemistry (Scheme 30a). Regrettably, styrene **666ag** proved to be too reactive under the reactions affording a complex mixture of oligomeric products under the reaction conditions. On the other hand, 2- and 4-vinylpyridines **666ah** and **666ai** proved much more amenable as coupling partners, generating the desired tertiary amine products **667ah** and **667ai** in 37% and 45% yield respectively. The more electrophilic 5-(trifluoromethyl)-2-vinylpyridine **666aj** furnished the corresponding aminopyridine **667aj** in a slightly improved 42% yield. 2-(1-(4-chlorophenyl)vinyl)pyridine **666ak** – combining the reactivity of both styrene and vinyl pyridine, served as an excellent alkene substrate, delivering the desired amine product **667ak** in 75% yield (2.3:1 d.r.). The diarylamine product is an analogue of the over-the-counter antihistamine drug chlorpheniramine. Both vinyl pyrazine **666al** and vinyl thiazole **666am** acceptors did not afford any of the desired heterocyclic amine products under the reaction conditions.



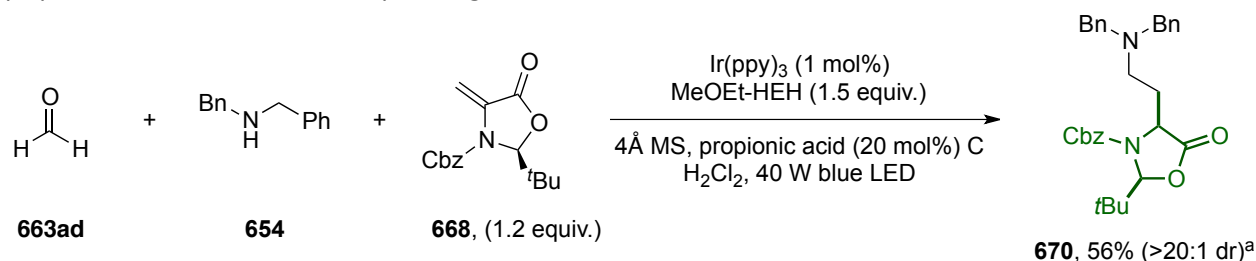
**Scheme 170** | Acceptor substrate scope for photocatalytic multicomponent synthesis of alkyl tertiary amines. Reactions conducted using Et-HEH unless otherwise stated. <sup>a</sup>Reaction conducted using amine:aldehyde:acceptor (1:1.1:1.1 equivalents). <sup>b</sup>Reaction conducted using amine:aldehyde:acceptor (1:2:2 equivalents). <sup>c</sup>Reaction conducted using MeOEt-HEH. <sup>d</sup>Reaction conducted by D. Reich

Amino acids play a pivotal role in both synthetic<sup>598,599</sup> and medicinal chemistry<sup>600</sup>. Despite the widespread use of peptides in therapeutic agents, there still remain significant challenges in the design of new peptide-based drugs due to low metabolic stability and poor physical properties<sup>601</sup>. One strategy for overcoming these hurdles is the substitution of native residues with unnatural amino acids<sup>602</sup>. Along these lines, chiral *tert*-butyl oxazolidinone **668**, first described by Beckwith<sup>603</sup> building upon the previous work of Karady<sup>604</sup> and Seebach<sup>605</sup> for the asymmetric synthesis of amino acids, was readily prepared on gram-scale (Scheme 171a). When combined with dibenzylamine **654** and paraformaldehyde **663ad**, it was found that radical addition followed by diastereoselective HAT from the less-hindered *Re*-face could be achieved with excellent diastereocontrol **669**, forming protected 2,4-diaminobutyric acid **670** in 56% yield (>20:1 d.r.) (Scheme 171b).

## (a) preparation of Karady-Beckwith alkene

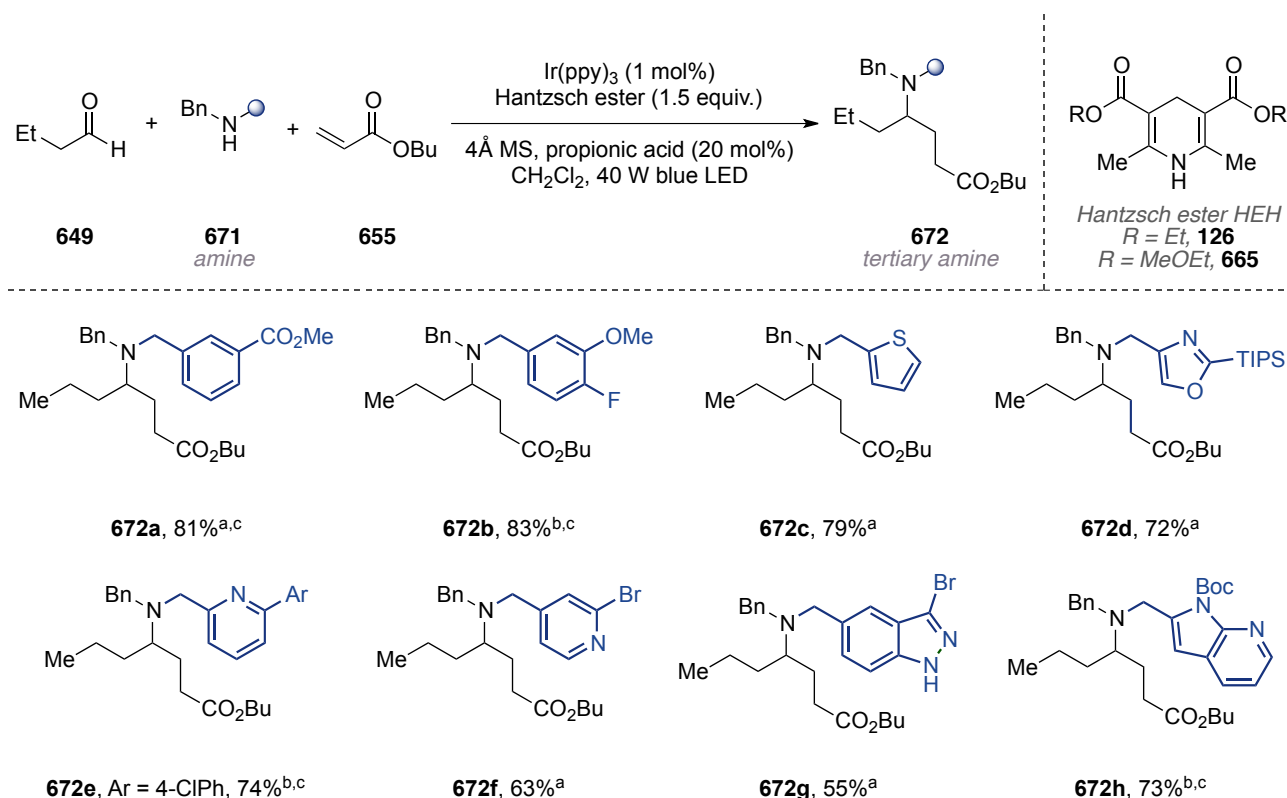


## (b) preparation of enantioenriched non-proteinogenic amino acids



**Scheme 171** | (a) Preparation of Karady-Beckwith alkene and proposed model for diastereoselectivity. (b) Diastereoselective reductive alkylation of benzaldehyde-derived iminium ions. <sup>a</sup>Reaction mixture pre-stirred at 45 °C for 1 hour in the dark prior to irradiation

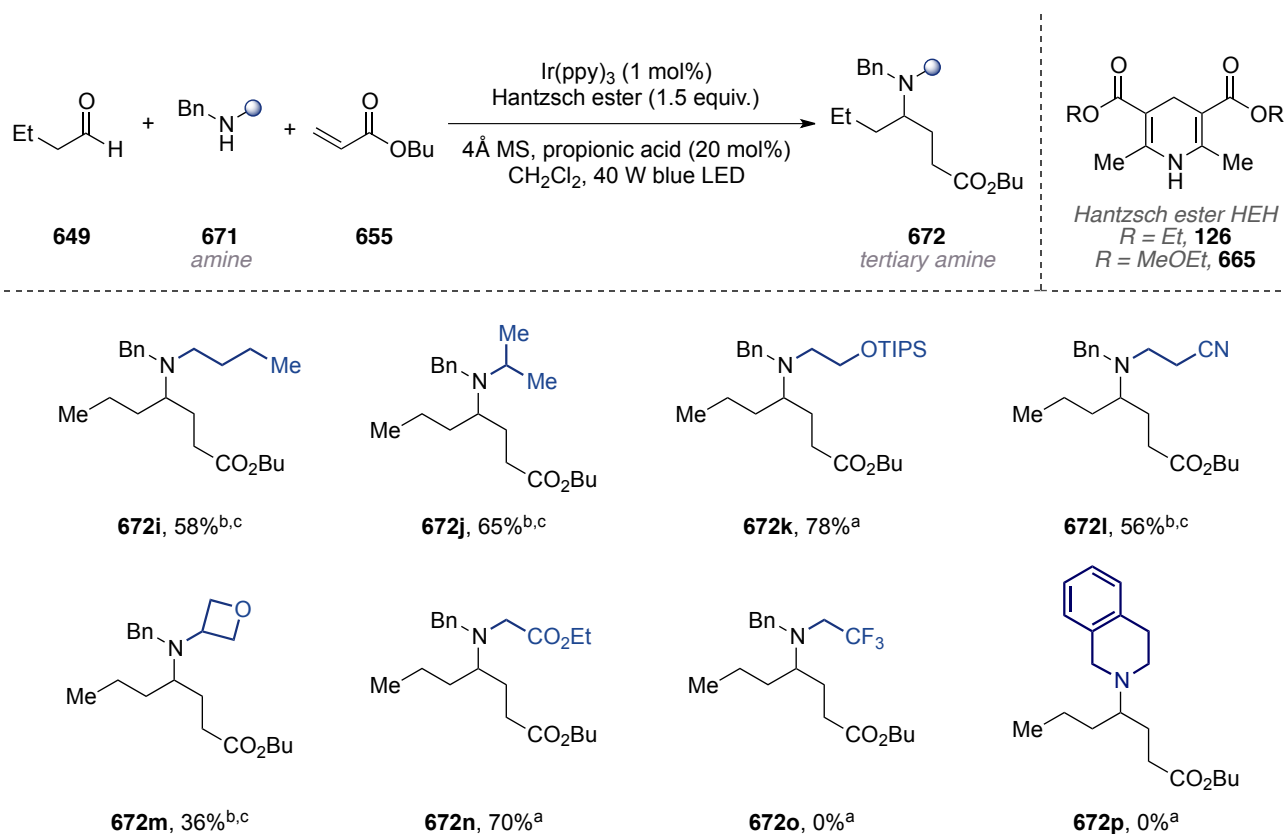
We next sought to investigate the scope of secondary amines compatible with the photocatalytic imine alkylation methodology. Substituted dibenzylamines **671a** and **671b** proved effective under the reaction conditions tolerating ester, methoxy and fluorine substituents in excellent yields **672a** and **672b** (81% and 83% respectively) (Scheme 172). Furthermore, electron-rich thiophene **671c** and acid-sensitive silyloxazole functionalities **671d** were tolerated in similarly high yields, affording the heteroaryl-substituted tertiary amines **672c** and **672d** in 79% and 72% yields. In addition, a range of Lewis basic heterocycles **671e–671h** proved particularly amenable as coupling partners, most notably with the inclusion of bromine substituents, which have been shown to undergo dehalogenation/radical coupling under similar conditions<sup>606</sup>.



**Scheme 172** | Amine substrate scope for photocatalytic multicomponent synthesis of alkyl tertiary amines. Reactions conducted using Et-HEH unless otherwise stated. <sup>a</sup>Reaction conducted using amine:aldehyde:acceptor (1:1.1:1.1 equivalents). <sup>b</sup>Reaction conducted using amine:aldehyde:acceptor (1:2:2 equivalents). <sup>c</sup>Reaction conducted using MeOEt-HEH

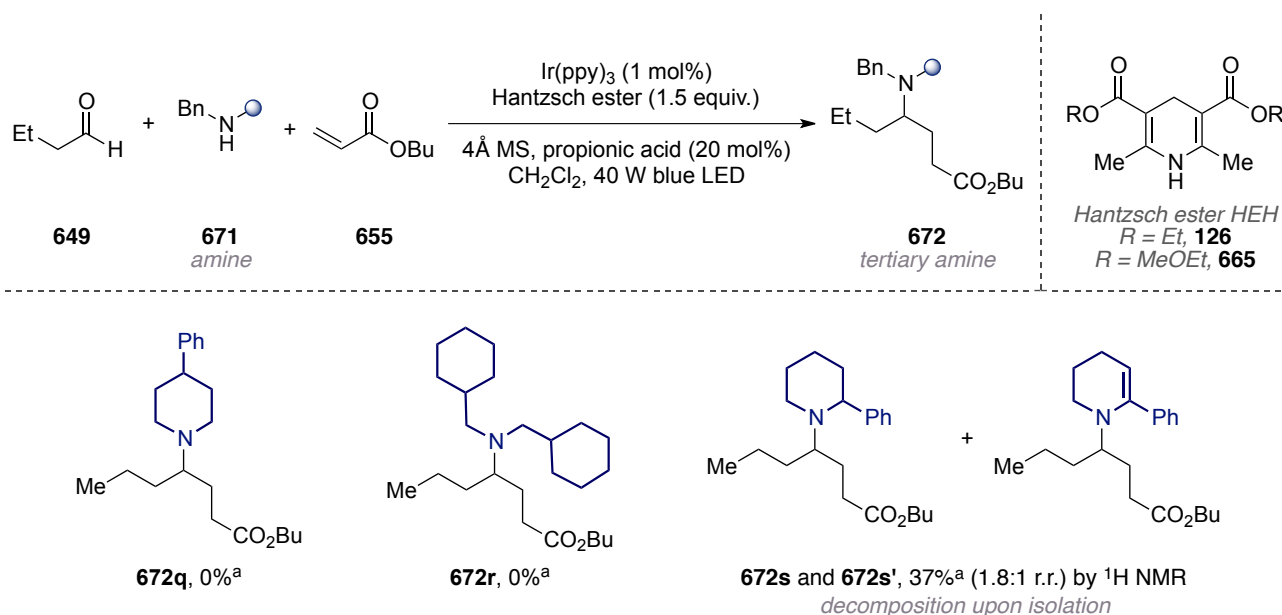
To further expand the utility of the process, a range of *N*-benzyl alkylamines were subjected to the reaction conditions (Scheme 173). Simple *N*-benzylbutylamine **671i** and *N*-benzylisopropylamine **671j** proved competent substrates, affording the tertiary amine products **672i** and **672j** in encouraging 65% and 78% yield respectively. Nevertheless, TIPS-protected *N*-benzylethanolamine **671k** and 3-(benzylamino)propanenitrile **671l** underwent smooth reductive alkylation, incorporating synthetically useful functional handles, **672k** and **672l**, in good 78% and 56% yield respectively. Moreover, acid-sensitive oxetanyl amine **671m** and less-nucleophilic *N*-benzylglycine ethyl ester **671n** were compatible with the reaction conditions, generating the amine products **672m** and **672n** in 36% and 70% yields. 2,2,2-Trifluoroethylbenzylamine **671o** did not form any of the desired tertiary amine product **672o**, no doubt due to the poor nucleophilicity of the amine<sup>607</sup>. In addition, tetrahydroisoquinoline **671p** underwent significant decomposition under the reaction conditions, presumably due to facile competing oxidative aromatization.





**Scheme 173** | Amine substrate scope for photocatalytic multicomponent synthesis of alkyl tertiary amines. Reactions conducted using Et-HEH unless otherwise stated. <sup>a</sup>Reaction conducted using amine:aldehyde:acceptor (1:1.1:1.1 equivalents). <sup>b</sup>Reaction conducted using amine:aldehyde:acceptor (1:2:2 equivalents). <sup>c</sup>Reaction conducted using MeOEt-HEH

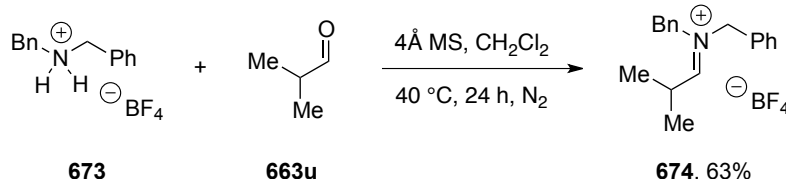
Having firmly established that synthetically versatile benzylamines were competent substrates, we sought to explore a variety of other dialkylamines architectures (Scheme 174). Immediately, it was identified that simple non-benzylic alkylamines, including 4-phenylpiperidine **671q** and the saturated isostructural bis(cyclohexylmethyl)amine **671r**, were incompatible with the methodology. Due to the complete consumption of starting materials, and complex reaction mixture profile, it was concluded that radical-based oligomerization had been the most likely outcome. At the same time, it was observed that 2-phenylpiperidine **671s** produced tertiary amine products **672s** and **672s'** with masses consistent with the loss of dihydrogen. Further analysis of the crude reaction mixture by  $^1\text{H}$  NMR indicated the likely formation of a conjugated enamine in the piperidine ring; however, repeated attempts to isolate the material proved unfruitful (*see* Appendix II, figure 12).



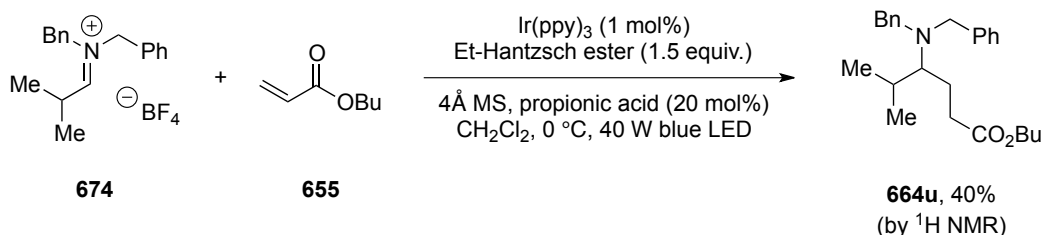
**Scheme 174** | Amine substrate scope for photocatalytic multicomponent synthesis of alkyl tertiary amines. Reactions conducted using Et-HEH unless otherwise stated. <sup>a</sup>Reaction conducted using amine:aldehyde:acceptor (1:1:1:1 equivalents).

The combination of these results led us to conclude that the benzylamine moiety was non-innocent in the transformation, potentially playing a crucial role in modulating the reactivity of radical addition.

(a) preparation of stable iminium salt



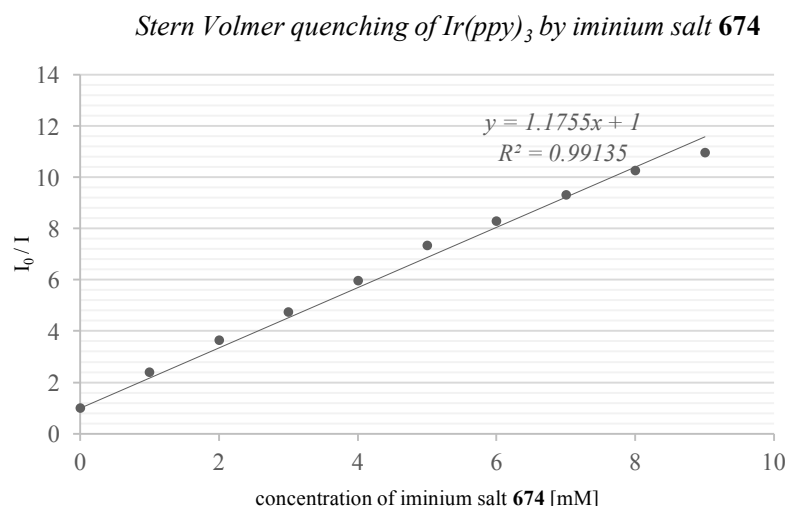
(b) photocatalytic reductive alkylation from pre-formed iminium ion



**Scheme 175** | (a) Preparation of stable ‘all-alkyl’ iminium ion. (b) Photocatalytic reductive alkylation from pre-formed iminium ion. Reactions conducted by D. Reich

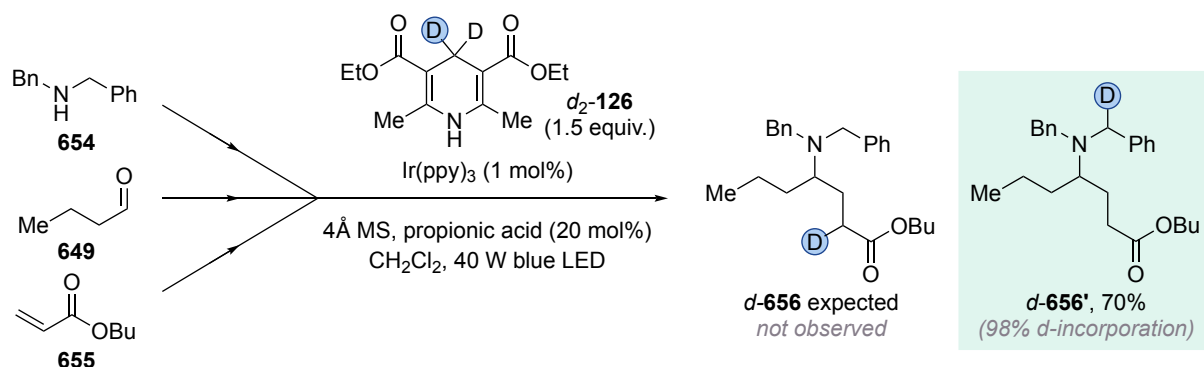
To further understand the mechanism of the transformation, the tetrafluoroborate salt of the iminium ion **674** derived from dibenzylamine salt **673** and isobutyraldehyde **663u** was isolated according to a modified procedure from Melchiorre and proved to be stable in solution (Scheme 175a)<sup>608</sup>. When subjected to the standard reaction conditions using *n*-butyl acrylate **655**, significant reduction of the iminium ion **674** was observed by GC-MS alongside trace product **664u**, presumably via polar reduction with Hantzsch ester – highlighting the importance of the enamine in protecting against this deleterious pathway. Critically, when irradiated at 0 °C the desired tertiary amine **664u** was formed

in 40% yield (by  $^1\text{H}$  NMR), confirming the iminium ion as an active intermediate in the catalytic cycle (Scheme 175b). Based on this, we undertook Stern Volmer quenching studies between the iminium ion **674** and  $\text{Ir}(\text{ppy})_3$  photocatalyst (Figure 6). The excited photocatalyst was effectively quenched by the iminium ion [ $k_q = 6.2 \times 10^5 \text{ L}\cdot\text{mol}^{-1}\text{s}^{-1}$  (see Appendix II, equation 1)]. It has been shown by MacMillan that enamines do not undergo reductive quenching with  $\text{Ir}(\text{ppy})_3$ <sup>609</sup>. Moreover, UV-Vis studies of the iminium ion **674** and Hantzsch ester **126** did not reveal the presence of an electron-donor acceptor (EDA) complex (see Appendix II, figure 11)<sup>610</sup>.



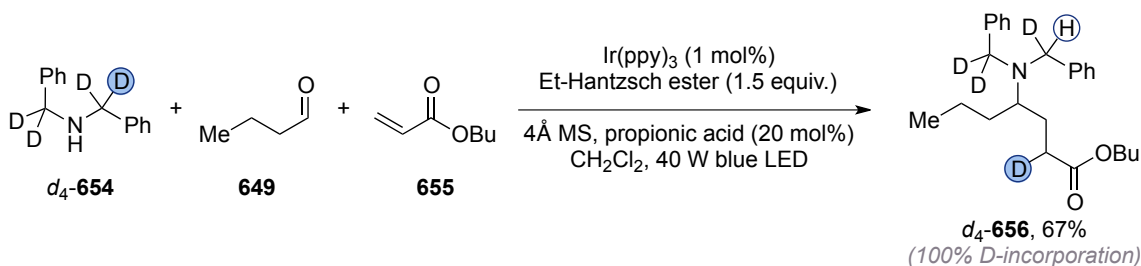
**Figure 6** | Stern Volmer quenching studies of  $\text{Ir}(\text{ppy})_3$  by iminium salt. Excitation at  $\lambda = 320 \text{ nm}$  and emission intensity recorded at  $\lambda = 518 \text{ nm}$

In establishing that the iminium ion serves as key intermediate, we wanted to ascertain the role of the benzyl group. To this end, 4,4- $d_2$ -Hantzsch ester  $d_2$ -**126** was prepared and substituted in the reaction between dibenzylamine **654**, butyraldehyde **649** and *n*-butyl acrylate **655**; the expected site of deuterium incorporation being at the  $\alpha$ -position to the ester carbonyl  $d$ -**656** (Scheme 176). Intriguingly, a single tertiary amine product was observed in 70% yield with a single deuterium incorporated at the  $\alpha$ -aminobenzylic position  $d$ -**656'**, potentially revealing that 1,5-HAT was occurring from the  $\alpha$ -ester radical to the benzylic protons.



**Scheme 176** | Deuteration studies for the photocatalytic reductive alkylation of iminium ions employing 4,4- $d_2$ -Hantzsch ester. Reaction conducted by D. Reich

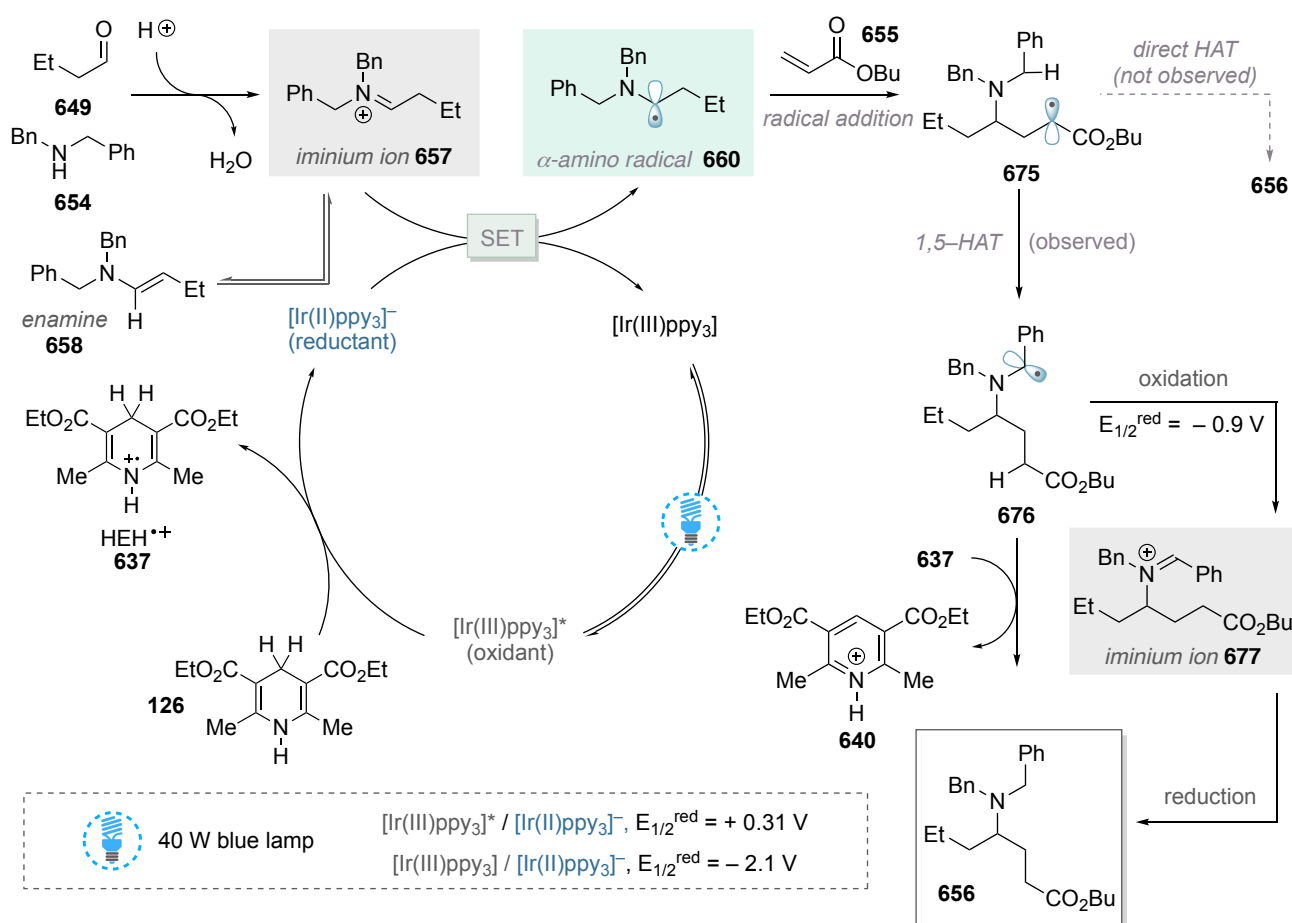
In order to exclude potential enolization H/D scrambling of the ester protons and/or oxidative deuteration of the tertiary amine product, bis(phenylmethyl- $d_2$ )amine  $d_4$ -**654** was prepared and subjected to the reaction conditions with 4,4- $H_2$ -Hantzsch ester **126** (Scheme 177). A single amine product  $d_4$ -**656** was obtained in 67% yield wherein one deuterium had transferred from the benzylamine unit to the  $\alpha$ -ester position.



**Scheme 177** | Deuteration studies for the photocatalytic reductive alkylation of iminium ions employing bis(phenylmethyl- $d_2$ )amine. Reaction conducted by D. Reich

Based on this evidence, our mechanistic proposal for the reaction begins with visible-light excitation of  $\text{Ir(ppy)}_3$  to the long-lived photoexcited  $^*\text{Ir(III)}$  species ( $\tau = 1.9 \mu\text{s}$ ) (Scheme 178)<sup>360</sup>. While this species may be sufficiently reducing  $[\text{Ir(IV)}/^*\text{Ir(III)}, E_{1/2}^{\text{red}} = -1.73 \text{ V vs. SCE in acetonitrile}]$ <sup>360</sup> to undergo SET to alkyl-iminium ion **657**, it has been reported that  $^*\text{Ir(III)ppy}_3$  is more effectively quenched by Hantzsch ester **126** [ $^*\text{Ir(III)}/\text{Ir(II)}, E_{1/2}^{\text{red}} = +0.31 \text{ V vs. SCE in acetonitrile}]$ <sup>360</sup> leading to  $[\text{Ir(II)ppy}_3]^-$  and the corresponding Hantzsch ester-radical cation **637** ( $k_q = 1.7 \times 10^7 \text{ L} \cdot \text{mol}^{-1} \text{ s}^{-1}$ )<sup>559</sup>. Importantly,  $[\text{Ir(II)ppy}_3]^-$  should be sufficiently reducing  $[\text{Ir(III)}/\text{Ir(II)}, E_{1/2}^{\text{red}} = -2.19 \text{ V vs. SCE in acetonitrile}]$ <sup>360</sup> to undergo SET with the full range of alkyl-iminium ions [ $E_{1/2}^{\text{red}} = -1.4$  to  $-2.0 \text{ V vs. SCE in acetonitrile}]$ <sup>552</sup>, providing a pathway to the  $\alpha$ -amino radical **660**. Radical addition to the electrophilic alkene **655** generates an  $\alpha$ -ester radical **675** which undergoes intramolecular 1,5-HAT to the benzylic position **676**. It can be reasoned that the formation of the benzylic radical acts as a strong thermodynamic driving force ( $\Delta G_{\text{stab}} \sim 16 \text{ kcal/mol}$ )<sup>611</sup>, inhibiting oligomerization of the  $\alpha$ -ester radical **675** (Scheme 180a). Liu and Gagosz have reported a similar approach for the non-

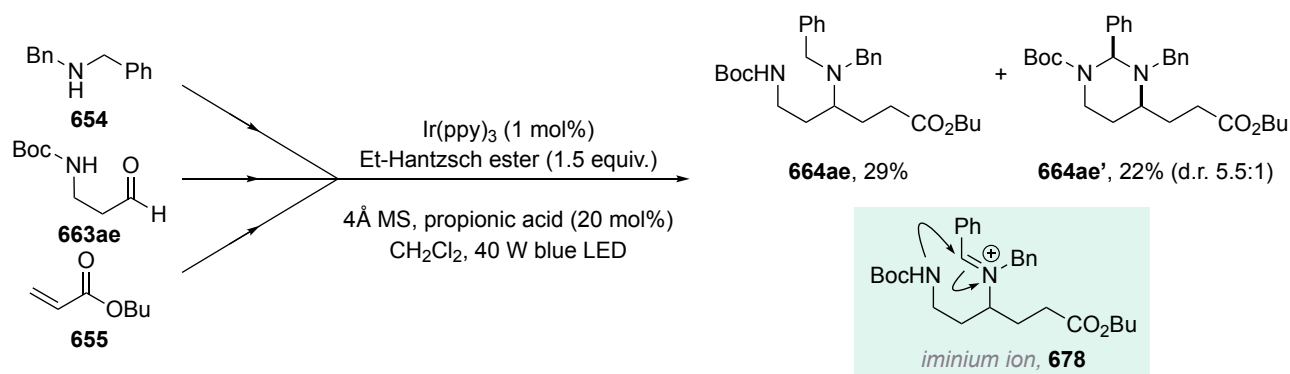
photoredox radical mediated trifluoromethylation of alkenes<sup>612–614</sup>. Reaction of the  $\alpha$ -aminobenzyl radical **676** with the Hantzsch ester-radical cation **637** could lead to the tertiary amine product and Hantzsch pyridine **640**. However, given the strongly reducing nature of the  $\alpha$ -aminobenzyl radical **676** [ $E_{1/2}^{\text{red}} = -0.9$  V vs. SCE (MeCN)]<sup>615</sup>, we were mindful that oxidation to the corresponding benzylidene iminium ion **677** could occur via an additional photoredox catalytic cycle. Subsequent polar or photocatalytic reduction of the iminium ion by Hantzsch ester leads to the tertiary amine product **656**. Interestingly, a mechanistic pathway whereby one iminium ion is transformed into a new iminium ion represents a formal redox-relay, which to the best of our knowledge, is unprecedented.



**Scheme 178** | Proposed mechanism for the photocatalytic reductive alkylation of iminium ions

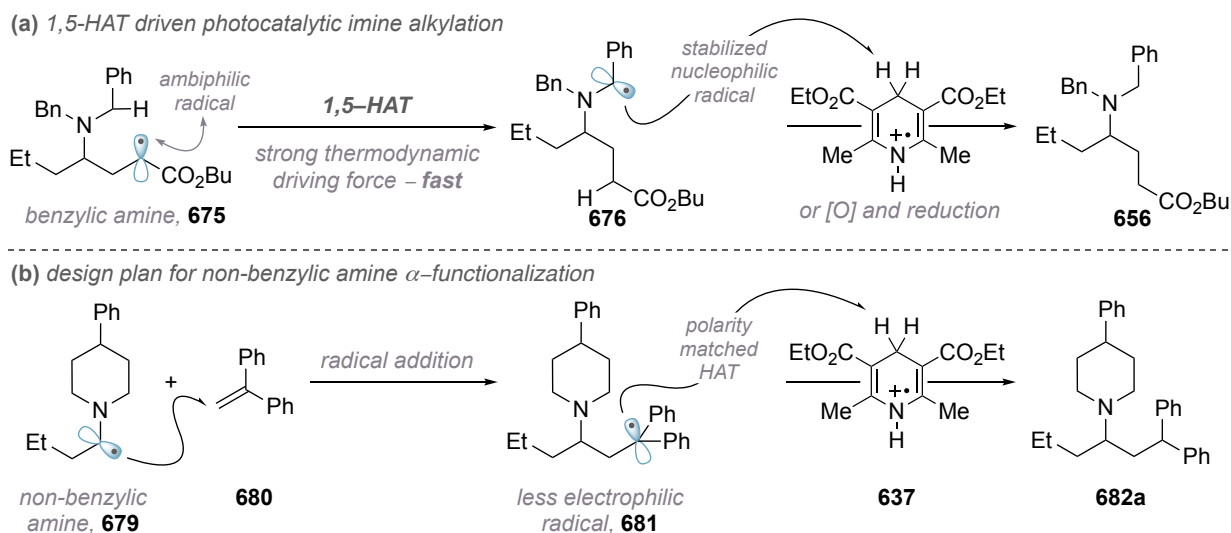
To ascertain the possible intermediacy of the benzylidene iminium ion **677**, it was hypothesized that an aldehyde bearing a pendant nucleophilic moiety may cyclize onto the benzylidene iminium ion intermediate prior to reduction **678** (Scheme 179). To test this, D. Reich subjected *N*-Boc-3-aminopropionaldehyde **663ae** to the reaction conditions; remarkably, a mixture of uncyclized **664ae** and cyclized products **664ae'** were obtained in a 51% yield in a 1.3:1 ratio. Moreover, the generation

of enamine by-products **672s'** when using 2-phenylpiperidine **671s** can be easily rationalized by the rapid deprotonation of the intermediate iminium ion (Scheme 174).



**Scheme 179** | Intramolecular cyclization of transiently generated iminium ion via redox-relay. Reaction conducted by D. Reich

Given the significantly higher quenching coefficient of Hantzsch ester **126** compared to the iminium ion **674**, as well as the mixture of products from the intramolecular trapping experiment (Scheme 179), it can be concluded that a reductive quenching pathway is likely to be operating, although a minor oxidative pathway cannot be ruled out. It should also be noted that while no product was obtained in the absence of photocatalyst, energy transfer from excited  $\text{Ir(ppy)}_3$  to Hantzsch ester **126** followed by single electron reduction of the iminium ion **657** by excited state Hantzsch ester cannot be discounted<sup>616,617</sup>. Notably, the excited state oxidation potential of Hantzsch ester has been shown to be up to  $E_{1/2}^{\text{ox}} \sim -2.28 \text{ V}$ <sup>618–621</sup>.

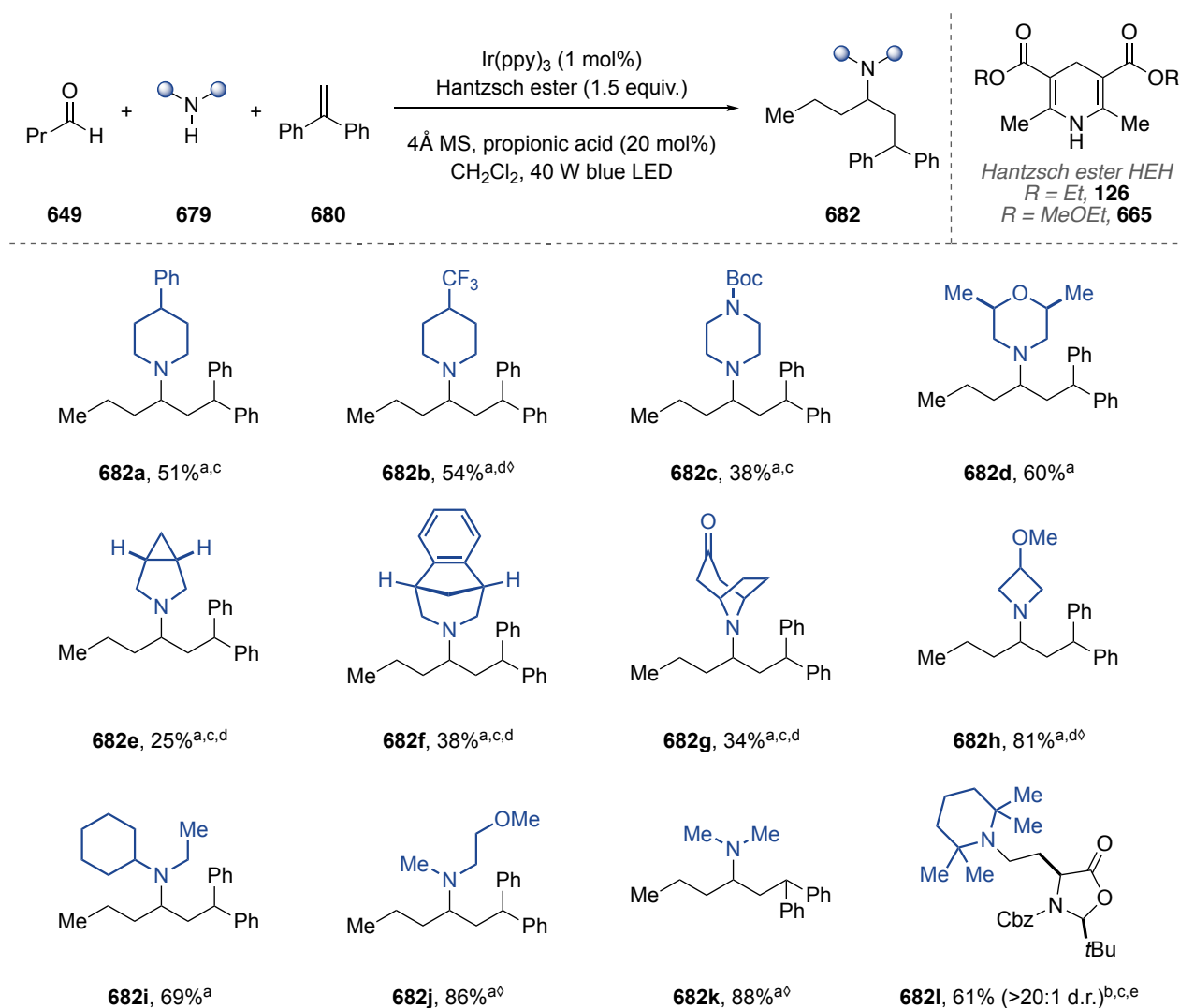


**Scheme 180** | (a) Mechanistic hypothesis for the 1,5-HAT driven reductive alkylation iminium ions. (b) Design plan for the reductive imine alkylation of non-benzylic amines

The utility of the benzylic 1,5-HAT operative in the redox-relay mechanism overcomes the inherent challenges posed by the intermolecular addition of  $\alpha$ -amino radicals to electrophilic alkenes (Scheme 180a). In addition, it provides a highly versatile protecting group that can be removed to reveal either

a primary or secondary alkylamine. Indeed, hydrogenolysis of the dibenzylamine group could be readily achieved using Pearlman's catalyst, affording butyl 4-aminoheptanonate **683** in 95% yield. Despite this, it was reasoned that by using an alkene that produces a less-electrophilic radical **681**, direct polarity-matched HAT with the Hantzsch ester-radical cation **637** may preclude the requisite 1,5-HAT process (Scheme 180b). This would facilitate the reaction of a wide variety of non-benzylic amine substrates **679**.

To test this, 4-phenylpiperidine **679a**, butyraldehyde **649** and 1,1-diphenylethylene **680** were combined under the standard photocatalytic conditions (Scheme 181). The desired tertiary amine product **682a** was obtained in a moderate 51% yield, in spite of the intrinsically-lower electrophilicity of the alkene acceptor. Importantly, this class of molecules are of paramount importance as H<sub>1</sub>-receptor antagonists<sup>622</sup>. The biological properties of the molecules can be tuned from antiallergics to cholergics, antipyretics, coronardilatics and antispasmodics<sup>623</sup>. Furthermore, 3,3-diarylpropylamines **123** have been shown to act as potent as sigma-1 receptor agonists, a key target in the development of therapeutics for neurodegenerative diseases<sup>624</sup>. A range of medicinally relevant secondary amines were trialled under the reaction conditions including piperazines, morpholines, azabicyclo[3.1.0]hexanes, azepines, tropinones and azetidines **679a–679h**, affording the functionalized tertiary amine products **682a–682h** in moderate to good yields (Scheme 181).

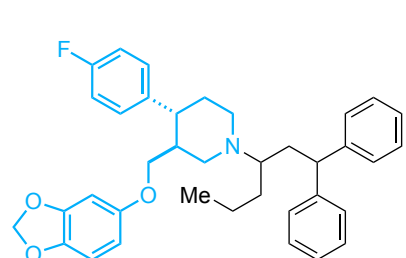
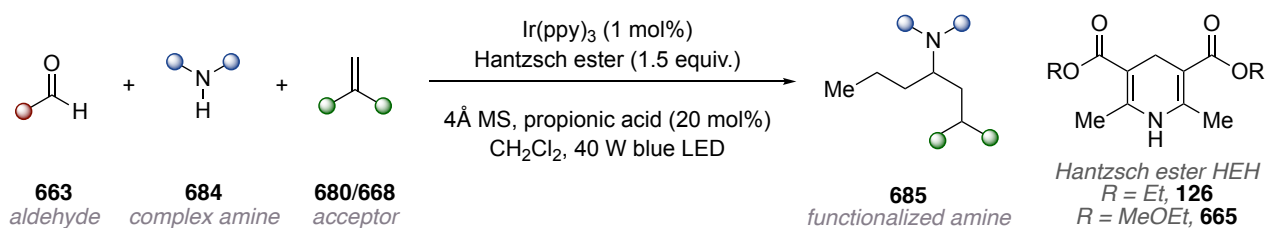


**Scheme 181** | Non-benzylic amine substrate scope for photocatalytic multicomponent synthesis of alkyl tertiary amines.

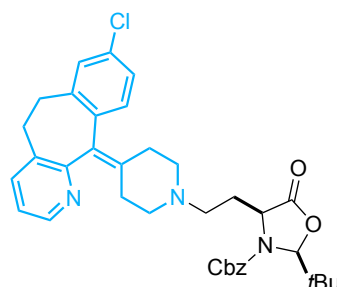
Reactions conducted using Et-HEH unless otherwise stated. <sup>a</sup>Reaction conducted using amine:aldehyde:acceptor (1:1.1:1.1 equivalents). <sup>b</sup>Reaction conducted using amine:aldehyde:acceptor (1:2:2 equivalents). <sup>c</sup>Reaction conducted using MeOEt-HEH. <sup>d</sup>Reaction conducted using amine hydrochloride salt and triethylamine (1 equiv.) <sup>e</sup>Reaction mixture pre-stirred at 45 °C for 1 hour in the dark prior to irradiation. <sup>o</sup>Reaction conducted by D. Reich

Moreover, the amine hydrochloride could be employed alongside one equivalent of triethylamine. Acyclic secondary amines **679i–679k**, including dimethylamine **679k**, were tolerated in similarly high yields. In addition to 1,1-diphenylethene **680**, chiral *tert*-butyl oxazolidinone **668** (95% e.e.) proved effective as an acceptor, facilitating the coupling between the hindered secondary amine TMP **295** and formaldehyde **663ad** in 61% yield (**682l**) (>20:1 d.r.). Acidic cleavage of the oxazolidinone furnished the enantioenriched TMP-derived amino acid in 95% yield (83% e.e. determined by Mosher acid method).

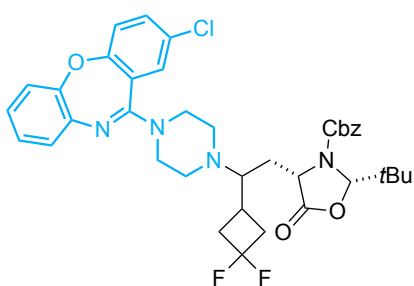




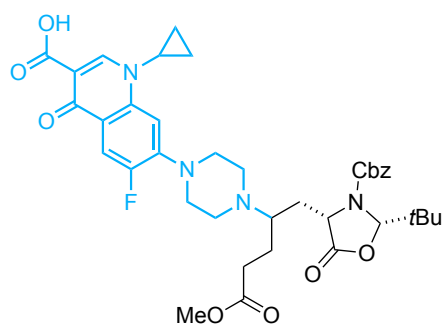
**685a**, 44% (d.r. 1:1)<sup>a,c,d</sup> from **paroxetine**



**685b**, 32%<sup>e,c</sup> from **desloratidine**



**685c**, 55% (d.r. 1:1)<sup>b,e</sup> from **amoxapine**



**685d**, 64% (d.r. 1:1)<sup>b,e,f</sup> from **ciprofloxacin**

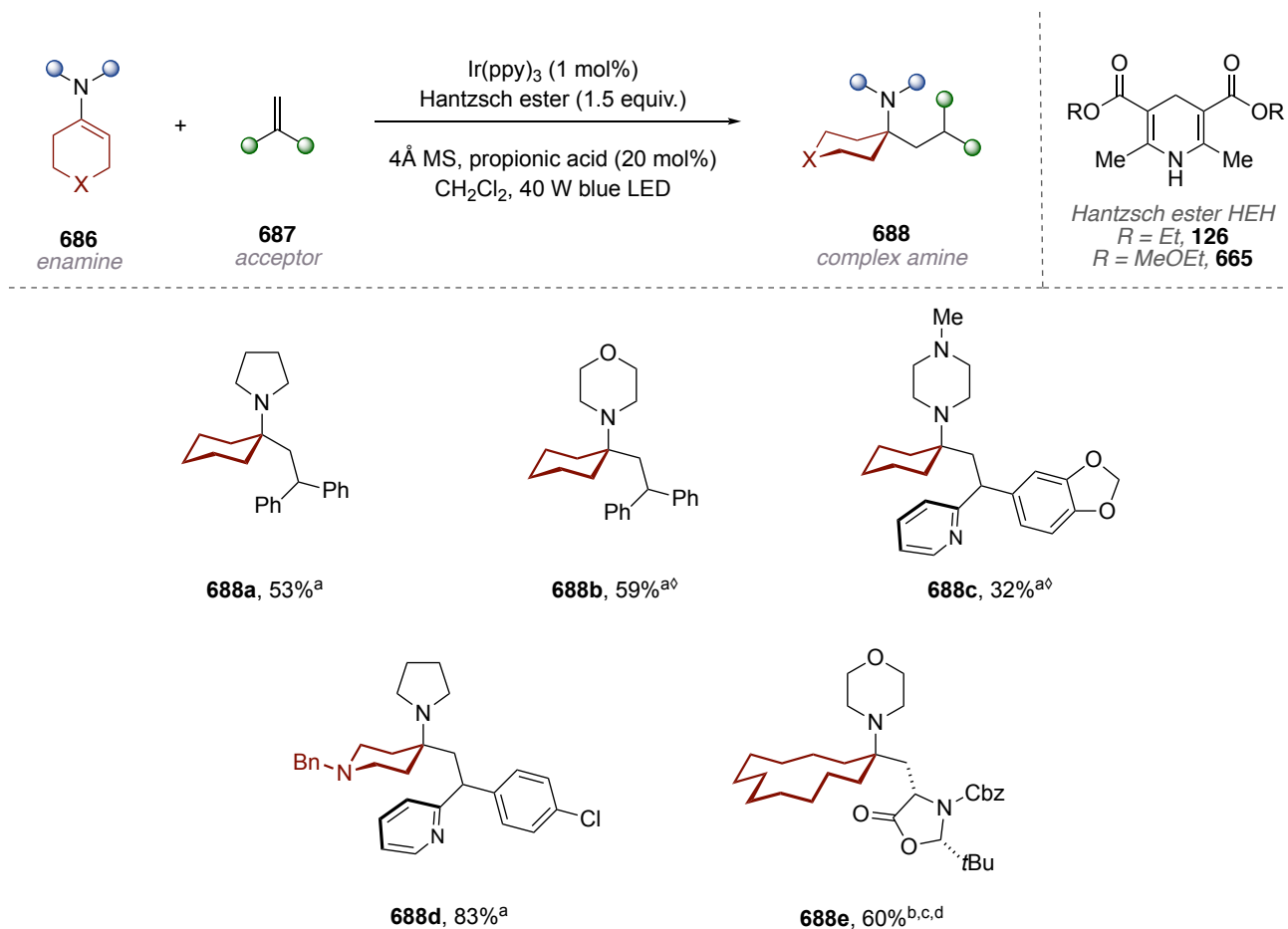
**Scheme 182** | Complex molecule substrate scope for photocatalytic multicomponent synthesis of alkyl tertiary amines.

Reactions conducted using Et-HEH unless otherwise stated. <sup>a</sup>Reaction conducted using amine:aldehyde:acceptor (1:1.1:1.1 equivalents). <sup>b</sup>Reaction conducted using amine:aldehyde:acceptor (1:2:2 equivalents). <sup>c</sup>Reaction conducted using MeOEt-HEH. <sup>d</sup>Reaction conducted using amine hydrochloride salt and triethylamine (1 equiv.). <sup>e</sup>Reaction mixture pre-stirred at 45 °C for 1 hour in the dark prior to irradiation. <sup>f</sup>Reaction conducted by D. Reich

Given that non-benzylic dialkylamines are common motifs amongst pharmaceuticals, a series functionally diverse small-molecule drugs were evaluated under the photocatalytic hydroaminoalkylation process (Scheme 182). Remarkably, upon coupling with a range of aldehydes **663** and acceptors **680** and **668**, piperidine-containing paroxetine **684a** (antidepressant) and desloratidine **684b** (antihistamine) furnished the corresponding functionalized amine products **685a** and **686b** in 44% and 32% yield respectively. Moreover, piperazine-containing amoxapine **684c** (antidepressant), and ciprofloxacin **684d** (antibiotic) – containing a redox-active quinolone moiety, underwent the desired multicomponent coupling to generate the amino acid functionalized products **685c** and **686d** in 55% and 64% yields.

Finally, it was considered that an important extension of the photocatalytic multicomponent process would be the use of ketones as coupling partners, generating  $\alpha$ -tertiary amine products **688**, a class of

compounds difficult to access using traditional methods<sup>508,509</sup>. Early attempts simply substituting acetone and cyclohexanone into the standard reaction proved fruitless, most likely due to the much more demanding condensation between secondary amines and ketones<sup>17</sup>. Given that enamines **658** were found to be the predominant species in the reaction mixture, we reasoned that using pre-formed ketone-derived enamines in the reaction would provide a more accessible source of alky-ketiminium ions. In addition, ‘Stork enamines’ **686** can be readily prepared on gram scale in one step, with many being commercially available<sup>625</sup>.



**Scheme 183** | Enamine substrate scope for photocatalytic multicomponent synthesis of  $\alpha$ -tertiary alkyl tertiary amines.

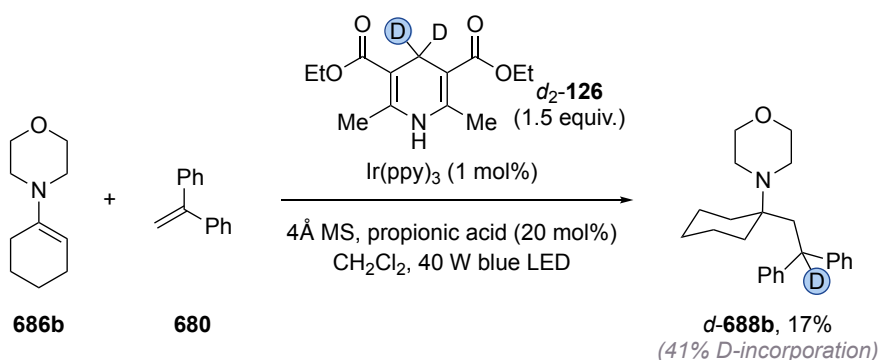
Reactions conducted using Et-HEH unless otherwise stated. <sup>a</sup>Reaction conducted using enamine:acceptor (1:2 equivalents). <sup>b</sup>Reaction conducted using enamine:acceptor (1:1.1 equivalents). <sup>c</sup>Reaction conducted using MeOEt-HEH.

<sup>d</sup>Reaction mixture pre-stirred at 45 °C for 1 hour in the dark prior to irradiation. <sup>†</sup>Reaction conducted by D. Reich

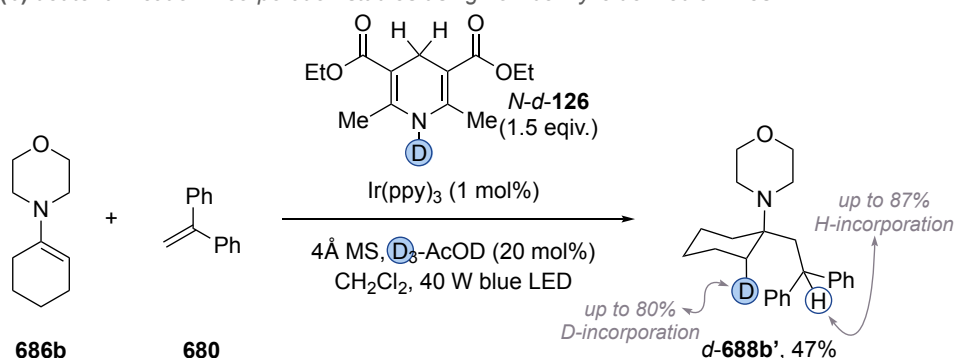
Pleasingly, pyrrolidine- and morpholine-derived cyclohexyl-enamines **686a** and **686b** underwent smooth coupling with 1,1-diphenylethylene **680**, affording the heavily-substituted tertiary amine products **688a** and **688b** in 53% and 59% yield respectively (Scheme 183). Moreover, piperazine- and piperidine-derived enamines **686c** and **686d** proved suitable coupling partners with pyridyl-derived vinyl arene acceptors **687c** and **666ak**, the electrophilic *p*-chlorophenyl substrate delivering the product **688d** in a good 83% yield. Hindered cyclododecyl enamine **686e** underwent hydroaminoalkylation with chiral oxazolidinone **668** in a good 63% yield.

In order to examine the mechanism of photocatalytic imine reductive alkylation using non-benzylic amines, morpholino-enamine **686b** and 1,1-diphenylethene **680** were subjected to the standard reaction conditions using 4,4-*d*<sub>2</sub>-Hantzsch ester *d*<sub>2</sub>-**126** (Scheme 184a). In line with our hypothesis that the generation of a less-electrophilic radical should favor direct reaction with the Hantzsch ester radical cation **637**, the deuterated tertiary amine product *d*-**688b** was obtained in 17% yield with 41% D-incorporation at the (*bis*)benzylic position. The low yield of the product is most likely due to the substantial KIE involved in hydrogen atom transfer reactions, resulting in deleterious side reactions<sup>626</sup>, as well as difficulties with H/D exchange during purification. Moreover, it is likely that D/H scrambling of the acidic (*bis*)benzylic position occurs under the reaction conditions, in particular upon treatment with molecular sieves<sup>627</sup>; however, reduction of the (*bis*)benzylic radical to the corresponding anion [ $E_{1/2}^{\text{red}} = -1.34$  V vs. SCE]<sup>628</sup> and subsequent protonation cannot be excluded. Finally, we investigated the reaction of morpholino-enamine **686b** and 1,1-diphenylethene **680** under standard conditions using *N*-*d*-Hantzsch ester *N*-*d*-**126** and *d*<sub>4</sub>-acetic acid (Scheme 184b).

(a) deuterium radical incorporation studies using non-benzylic derived amines



(b) deuterium cation incorporation studies using non-benzylic derived amines



**Scheme 184** | (a) Deuteration studies for the photocatalytic reductive alkylation of non-benzylic iminium ions employing 4,4-*d*<sub>2</sub>-Hantzsch ester. (b) Deuteration studies for the photocatalytic reductive alkylation of iminium ions employing *N*-*d*-Hantzsch ester and *d*<sub>3</sub>-AcOD. Reactions conducted by D. Reich

As HAT from Hantzsch ester **126** occurs from the 4-position, we would expect only hydrogen to be incorporated at the (*bis*)benzylic position. On the converse, all of the available acidic protons are deuterons and so D-incorporation would be expected to occur exclusively at the enamine  $\beta$ -position.

Pleasingly, the tertiary amine product *d*-**688b'** was furnished in 47% yield with up to 80% D-incorporation at the enamine  $\beta$ -position and up to 87% H-incorporation at the (*bis*)benzylic position.

#### 5.4 Summary

This chapter has detailed the development of a general strategy for the photocatalytic multicomponent synthesis of complex tertiary alkylamines. This methodology is able to leverage all-alkyl  $\alpha$ -amino radicals, generated from multiple abundant feedstocks, in a distinct C–C bond forming. Employing visible light photoredox catalysis, a series of *in-situ* generated alkyl aldiminium and ketiminium ions can be reduced regiospecifically to the corresponding  $\alpha$ -amino radicals, overcoming the fundamental limitations in selectivity associated with oxidative process. Mechanistic studies including D-incorporation and Stern-Volmer quenching elucidated the mechanism, identifying a remarkable 1,5-HAT process was operating between the  $\alpha$ -ester radical and benzylamine methylene position, acting as a thermodynamic driving force for the reaction and inhibiting deleterious polymerization. Oxidation of the  $\alpha$ -aminobenzyl radical to the benzyliiminium ion and subsequent reduction by Hantzsch ester generates the tertiary amine products – constituting a unique redox-relay of iminium ions. The reaction was found to be general across a range of complex substrates (>60 examples); moreover, by the modulating the electronics of the acceptor, complex medicinally relevant non-benzylic amines could be tolerated in good yields.

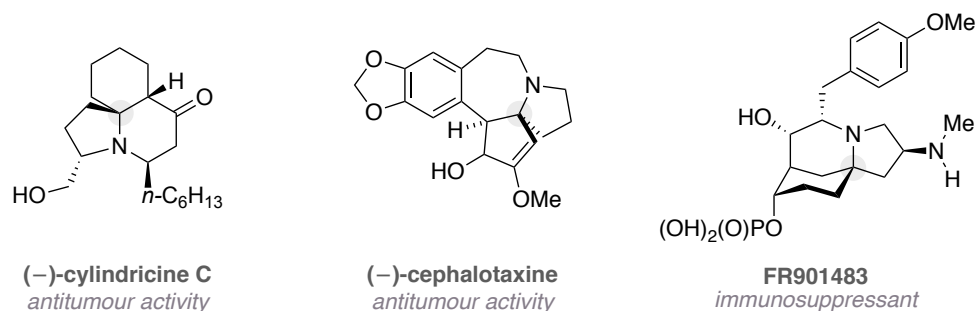
## 5 Conclusion and Outlook

Over the last two decades, transition metal catalysis has emerged as one of the most effective platforms for the synthesis and functionalization of alkylamines. During this time, several areas have continued to produce advances at the highest level, for example, hydroamination, C–H activation, and photoredox catalysis, and consequently have become (or are becoming) the cornerstones of modern amine synthesis.

Despite these advances, transformations on aliphatic amines remain rare and often require bespoke protecting groups in order to modulate the nucleophilicity of the amine motif. Nowhere is this more apparent than in C–H activation, for which there are currently no direct methods that can selectively target methylene C–H bonds in the  $\beta$ -position to an alkylamine. Based on these challenges, we have developed a systematic method for the selective  $\beta$ -functionalization of readily accessible alkylamines, forming *trans*-disubstituted  $\beta$ -lactams in high yields and diastereoselectivities. The reaction was found to be applicable to a wide range of aliphatic amine substrates with exceptional functional group tolerance as well as displaying remarkable selectivity for amines bearing multiple similar methylene C–H bond environments. Mechanistic studies revealed that the unique combination of reaction conditions enables the formation of a unique Pd<sup>II</sup>-carbamoyl intermediate; however, it is believed that by tailoring these parameters, remote and transannular  $\gamma$ - and  $\delta$ -C–H bonds could be targeted, accessing a more diverse array of amine products. Moreover, given the remarkable dependence on Xantphos-derived ligands, we anticipate that the use of a chiral Xantphos ligand may give rise to enantiopure  $\beta$ -lactam products.

During our research to further explore this carbonylation platform, we discovered that  $\alpha$ -tertiary amines (ATAs), possessing both a  $\beta$ -methyl C–H bond and  $\beta$ -methylene C–H bond underwent exclusive carbonylation at the traditionally less reactive and more hindered methylene position. Using conditions developed for amine methylene C–H carbonylation, this unprecedented reactivity was relayed across a range of ATA scaffolds. Pivotal to the success of this selective C–H carbonylation is the presence of a fully-substituted carbon atom on one side of the amine linkage, which directs the reaction to the C–H bond adjacent to the ATA motif. This methodology enabled the functionalization of biologically important yet highly reactive *N*-methyl amines, as well as first example of a Pd-catalyzed C–H activation that is selective for  $\beta$ -methylene C–H bonds in the presence of highly reactive and accessible  $\gamma$ -C(*sp*<sup>2</sup>)–H bonds on an aromatic ring. Given the

remarkable functional group tolerance and selectivity, combined with the synthetic challenges of accessing complex ATAs, this methodology is currently being implemented in the total synthesis of two alkaloids with antitumour activity: (–)-cylindricine C and (–)-cephalotaxine (Figure 7).



**Figure 7** | Total synthesis targets for Pd-catalyzed ATA carbonylation and photocatalytic reductive imine alkylation

$\alpha$ -Amino radicals have become one of the most important reactive intermediates of recent times for the synthesis of complex amines. However, within the purview of photoredox catalysis, the limitations of accessing all-alkyl  $\alpha$ -amino radicals has been clearly demonstrable due to the fundamental lack of selectivity in oxidative processes. On the converse, reductive processes are much more scarce, despite allowing complete regiocontrol of the resulting radical. Notwithstanding these challenges, we have developed the first photocatalytic reductive alkylation of all-alkyl iminium ions for the synthesis of tertiary amines. In this multi-component reaction, a visible-light-mediated single-electron reduction of *in-situ* generated iminium ions furnishes distinct  $\alpha$ -amino radicals, which engage simple alkenes and lead to carbon-carbon bond formation. The reaction proceeds under mild conditions, exhibits broad functional group tolerance within each component, and enables the synthesis of tertiary amines not readily accessible by existing methods. Due to the unique range of  $\alpha$ -amino radicals accessible under this manifold, efforts are currently underway to intercept this reactive intermediate with unactivated alkenes both inter- and intramolecularly, introduce transition metal catalysts in order to facilitate new C–C bond forming processes, and promote the ring opening of adjacent strained carbocycles. Moreover, we plan to extend this methodology to incorporate primary amines via the SET of protonated imines – with the view to developing an asymmetric reductive alkylation protocol. Initial results have proved promising and are currently being applied in the total synthesis of the potent immunosuppressant FR901483 (Figure 7).

## 6 Experimental Procedures

### 6.1 General Experimental

All reactions were run under an inert atmosphere ( $N_2$ ) unless otherwise stated, with oven-dried glassware, using standard techniques. Anhydrous solvents were obtained from solvent stills (diethyl ether was distilled from sodium triphenylmethane ketyl; tetrahydrofuran from lithium aluminium hydride; acetonitrile, dichloromethane, hexane and toluene from calcium hydride). Dichloromethane for use in the photocatalytic reaction was dried using 4Å MS (beads), degassed (Freeze-pump-thaw) and stored in a Schlenk flask under  $N_2$ . No appreciable deterioration in yield was observed after use for 3 months. Similar results were obtained using commercial anhydrous dichloromethane. Powdered 4Å MS were activated prior to use by prolonged heating (250 °C) under hi-vacuum (1 mbar) and stored in a round-bottomed flask under  $N_2$ . No appreciable deterioration in yield was observed after use for 3 months. Similar yields were obtained using commercially available activated powdered 4Å MS. Aldehydes were used as supplied if sufficiently pure otherwise they were purified either by distillation or flash column chromatography and used immediately. All acceptor alkenes containing stabilizer were distilled prior to use and stored at 5 °C. No appreciable deterioration in yield was observed after storage for 3 months.  $Ir(ppy)_3$  was obtained from Sigma-Aldrich and used as supplied. Amines were used as supplied if sufficiently pure otherwise they were purified either by distillation or flash column chromatography and used immediately. Et-Hantzsch ester (Et-HEH) was obtained from Matrix Scientific and used without further purification. All other commercial reagents were used as supplied unless otherwise stated. Silver pivalate ( $AgOPiv$ ) was prepared according to a literature procedure<sup>629</sup>.

Irradiation of the reaction mixture was achieved using a Kessil A160WE LED – Tuna blue aquarium light (setup: max blue, max intensity). Optimization was conducted using a standard 30W CFL bulb. Clear glass vials (4 mL) with PTFE/silicon septum lined screw caps were used as the standard reaction vessel (VWR catalogue number 548-0521).

Analytical thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 F254 0.20 mm precoated, glass backed silica gel plates. Visualisation of the developed chromatogram was performed by UV absorbance ( $\lambda_{max} = 254$  nm), and/or by aqueous  $KMnO_4$ . Flash column chromatography was performed using silica gel (Merck Geduran Si 60 [40-63  $\mu m$ ]) with the indicated solvent system.

Stern-Volmer quenching was performed using a Shimadzu RF-6000 spectrofluorometer.

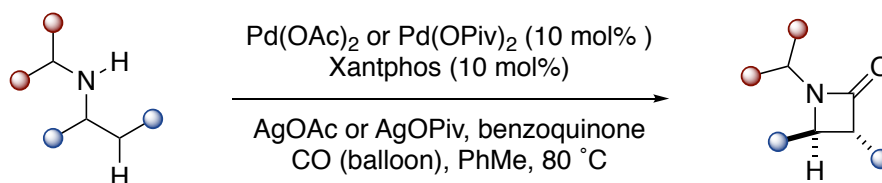
Experiments were recorded using a quartz cell equipped with septa-lined screw cap under Ar. UV-Vis analysis was performed on a Shimadzu UV-1800 spectrophotometer.

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX 400 or DPX 500 spectrometer with cryoprobe. Chemical shifts ( $\delta$ ) for  $^1\text{H}$  NMR spectra are recorded in ppm from  $\text{Me}_4\text{Si}$  with the solvent resonance as the internal standard ( $\text{CDCl}_3 = 7.26$  ppm,  $\text{DMSO}-d_6 = 2.50$  ppm,  $\text{C}_6\text{D}_6 = 7.16$  ppm,  $\text{MeOH}-d_4 = 3.31$  ppm,  $\text{D}_2\text{O} = 4.79$  ppm). Data is reported as follows: chemical shift [integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, sxt = sextet, spt = septet, m = multiplet, br = broad), coupling constant and molecular assignment].  $^{13}\text{C}$  NMR spectra are reported in ppm from  $\text{Me}_4\text{Si}$  with the solvent resonance as the internal standard ( $\text{CDCl}_3 = 77.16$  ppm,  $\text{DMSO}-d_6 = 39.52$  ppm,  $\text{C}_6\text{D}_6 = 128.06$  ppm,  $\text{MeOH}-d_4 = 49.00$  ppm).  $^{19}\text{F}$  NMR spectra are reported in ppm from  $\text{CFCl}_3$  and are uncorrected.  $^{31}\text{P}$  NMR spectra are reported in ppm from 85%  $\text{H}_3\text{PO}_4$  and are uncorrected.

Infrared spectra (FT-IR) were recorded using a Perkin-Elmer Paragon 1000 Fourier transform Spectrometer equipped with ATR and analysed as thin films, with absorption maxima ( $\nu_{\text{max}}$ ) being quoted in wavenumbers ( $\text{cm}^{-1}$ ) and characteristic peaks being defined (s = strong, br = broad). High Resolution Mass spectrometry (HRMS) was carried out by the ESPRC Mass Spectrometry Service at the University of Swansea using an LTQ Orbitrap XL spectrometer with positive ion nano-electrospray. Melting points (m.p.) were recorded using a Gallenkamp melting point apparatus and are reported uncorrected.

## 6.2 Experimental Procedures for the Synthesis of $\beta$ -lactams

### General Procedure A for the Synthesis of $\beta$ -lactams

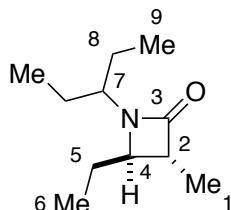


To a 10 mL oven-dried round-bottomed flask with large oval stirrer bar was added  $\text{Pd}(\text{OAc})_2$  or  $\text{Pd}(\text{OPiv})_2$  (0.03 mmol, 0.1 equiv.),  $\text{AgOAc}$  or  $\text{AgOPiv}$  (0.9 mmol, 3 equiv.), Xantphos (17 mg, 0.03 mmol, 0.1 equiv.) and 1,4-benzoquinone (65 mg, 0.6 mmol, 2 equiv.). Anhydrous toluene (3 mL) and amine (0.3 mmol, 1 equiv.) were added successively and the flask sealed with a new septum and Teflon tape. A balloon of carbon monoxide was placed on top and the flask evacuated and backfilled (3 cycles). The flask was then placed into a preheated oil bath at  $80^\circ\text{C}$  so as the solvent and oil level



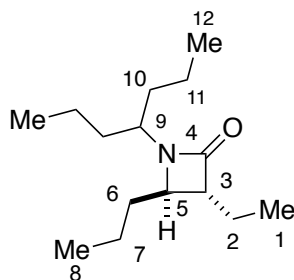
matched and left to stir at 500 rpm for 18 hours. After such time, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (2 mL). The mixture was filtered over celite and washed with additional ethyl acetate (5 mL). The organics were removed *in vacuo* and the crude reaction mixture purified by flash column chromatography on silica gel to afford the corresponding  $\beta$ -lactam.

*trans*-4-ethyl-3-methyl-1-(pentan-3-yl)azetidin-2-one **493**



Prepared according to general procedure A using di(pentan-3-yl)amine **492** (47.1 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 5% ethyl acetate in petroleum ether to 20% ethyl acetate in petroleum ether) and filtration over activated charcoal gave the title compound as a colourless oil (45.5 mg, 83%, d.r. = 12:1).  $R_f$  (30% ethyl acetate in petroleum ether): 0.52; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2960, 2929, 2873, 1740, 1459, 1397, 1372, 1352;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.29 (1 H, q,  $J = 7.0$  Hz,  $\text{H}_7$ ), 3.07 (1 H, dd,  $J = 2.0, 10.0$  Hz,  $\text{H}_4$ ), 2.68 (1 H, dq,  $J = 2.5, 7.5$  Hz,  $\text{H}_2$ ), 1.90 – 1.82 (1 H, m,  $\text{H}_{8a}$ ), 1.60 – 1.42 (5 H, m,  $\text{H}_5$ ,  $\text{H}_{8a''}$  and  $\text{H}_{8b}$ ), 1.29 (3 H, d,  $J = 7.5$  Hz,  $\text{H}_1$ ), 0.95 – 0.91 (9 H, m,  $\text{H}_6$  and  $\text{H}_9$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 171.4 ( $\text{C}_3$ ), 61.2 ( $\text{C}_4$ ), 56.1 ( $\text{C}_7$ ), 49.2 ( $\text{C}_2$ ), 27.6 ( $\text{C}_{8a}$ ), 27.3 ( $\text{C}_{8b}$ ), 25.5 ( $\text{C}_5$ ), 14.0 ( $\text{C}_1$ ), 11.5 ( $\text{C}_{9a}$ ), 11.4 ( $\text{C}_{9b}$ ), 10.1 ( $\text{C}_6$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  186.1695,  $\text{C}_{11}\text{H}_{22}\text{NO}$  requires 186.1696;  $^1\text{H}$  Selective NOESY (500.1 MHz,  $\text{C}_6\text{D}_6$ , mixing time = 1.40 s) Irradiating  $\text{H}_4$  (2.66 Hz) positive NOE correlation at  $\text{H}_1$  (1.10 Hz) = 5.2%.

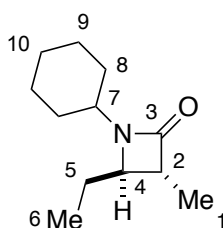
*trans*-3-ethyl-1-(heptan-4-yl)-4-propylazetidin-2-one **524a**



Prepared according to general procedure A using di(heptan-4-yl)amine **523a** (64.0 mg, 0.5 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 20% ethyl

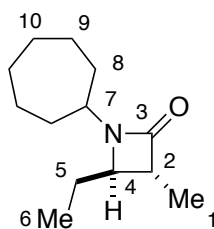
acetate in petroleum ether) and filtration over activated charcoal gave the title compound as a colourless oil (59 mg, 82%, d.r. > 20:1).  $R_f$  (10% ethyl acetate in petroleum ether): 0.30; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2959, 2931, 2875, 1739, 1461, 1394.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.48 (1 H, spt,  $J = 4.5$  Hz,  $\text{H}_9$ ), 3.21 – 3.17 (1 H, m,  $\text{H}_5$ ), 2.59 (1 H, dt,  $J = 2.0, 6.2$  Hz,  $\text{H}_3$ ), 1.84 – 1.32 (14 H, m,  $\text{H}_2$ ,  $\text{H}_6$ ,  $\text{H}_7$ ,  $\text{H}_8$  and  $\text{H}_{11}$ ), 1.04 – 0.91 (12 H, m,  $\text{H}_1$ ,  $\text{H}_8$  and  $\text{H}_{12}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 170.5 ( $\text{C}_4$ ), 57.8 ( $\text{C}_5$ ), 56.5 ( $\text{C}_3$ ), 52.2 ( $\text{C}_9$ ), 37.2 ( $\text{C}_{10a}$ ), 36.6 ( $\text{C}_6$ ), 34.9 ( $\text{C}_{10b}$ ), 22.3 ( $\text{C}_2$ ), 20.1 ( $\text{C}_{11a}$ ), 20.1 ( $\text{C}_{11b}$ ), 19.6 ( $\text{C}_7$ ), 14.4 ( $\text{C}_8$ ), 14.1 ( $\text{C}_{12a}$ ), 14.0 ( $\text{C}_{12b}$ ), 12.1 ( $\text{C}_1$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  240.2320,  $\text{C}_{15}\text{H}_{30}\text{NO}$  requires 240.2322.

*trans*-1-cyclohexyl-4-ethyl-3-methylazetidin-2-one **479**



Prepared according to general procedure A using *N*-(pentan-3-yl)cyclohexanamine **477** (50.8 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 2.5% ethyl acetate in petroleum ether to 20% ethyl acetate in petroleum ether with 1%  $\text{NH}_4\text{OH}$ ) and filtration over activated charcoal gave the title compound as a colourless oil (42.7 mg, 73%, d.r. > 20:1).  $R_f$  (20% ethyl acetate in petroleum ether): 0.31; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2929, 2855, 1740, 1452, 1395, 1371, 1323, 1259, 1217;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.42 (1 H, tt,  $J = 3.9, 11.7$  Hz,  $\text{H}_7$ ), 3.14 (1 H, dd,  $J = 2.7, 9.4$  Hz,  $\text{H}_4$ ), 2.64 (1 H, dq,  $J = 2.0, 7.4$  Hz,  $\text{H}_2$ ), 1.91 – 1.10 (15 H, m,  $\text{H}_1$ ,  $\text{H}_5$ ,  $\text{H}_8$ ,  $\text{H}_9$  and  $\text{H}_{10}$ ), 0.93 (3 H, t,  $J = 7.4$  Hz,  $\text{H}_6$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 170.4 ( $\text{C}_3$ ), 60.7 ( $\text{C}_4$ ), 51.5 ( $\text{C}_7$ ), 48.8 ( $\text{C}_2$ ), 32.4 ( $\text{C}_8$ ), 30.9 ( $\text{C}_{10}$ ), 27.2 ( $\text{C}_5$ ), 25.5 ( $\text{C}_{9a}$ ), 25.5 ( $\text{C}_{9b}$ ), 13.6 ( $\text{C}_1$ ), 9.7 ( $\text{C}_6$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  196.1691,  $\text{C}_{12}\text{H}_{22}\text{NO}$  requires 196.169

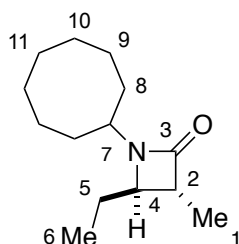
*trans*-1-cycloheptyl-4-ethyl-3-methylazetidin-2-one **524b**



Prepared according to general procedure A using *N*-(pentan-3-yl)cycloheptanamine **523b** (55.0 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to

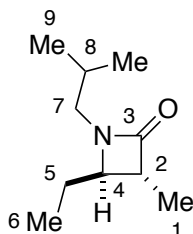
20% ethyl acetate in petroleum ether) and filtration over activated charcoal gave the title compound as a colourless oil (42.0 mg, 67%, d.r. > 15:1).  $R_f$  (10% ethyl acetate in petroleum ether): 0.18; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2925, 2859, 1457, 1734, 1392, 1361, 1323;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.42 (1 H, tt,  $J = 3.9, 11.7$  Hz,  $\text{H}_7$ ), 3.14 (1 H, dd,  $J = 2.7, 9.4$  Hz,  $\text{H}_4$ ), 2.64 (1 H, dq,  $J = 2.0, 7.4$  Hz,  $\text{H}_2$ ), 1.91 – 1.10 (17 H, m,  $\text{H}_1, \text{H}_5, \text{H}_8, \text{H}_9$  and  $\text{H}_{10}$ ), 0.93 (3 H, t,  $J = 7.4$  Hz,  $\text{H}_6$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 170.4 ( $\text{C}_3$ ), 60.7 ( $\text{C}_4$ ), 51.5 ( $\text{C}_7$ ), 48.8 ( $\text{C}_2$ ), 32.4 ( $\text{C}_{8a}$ ), 30.9 ( $\text{C}_{8b}$ ), 27.2 ( $\text{C}_{10}$ ), 25.5 ( $\text{C}_5$ ), 25.5 ( $\text{C}_9$ ), 13.6 ( $\text{C}_1$ ), 9.7 ( $\text{C}_6$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  210.1849,  $\text{C}_{13}\text{H}_{24}\text{NO}$  requires 210.1852.

*trans*-1-cyclooctyl-4-ethyl-3-methylazetidin-2-one **524c**



Prepared according to general procedure A using *N*-(pentan-3-yl)cyclooctanamine **523c** (59.2 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 20% ethyl acetate in petroleum ether) and filtration over activated charcoal gave the title compound as a colourless oil (31.8 mg, 51%, d.r. > 7:1).  $R_f$  (10% ethyl acetate in petroleum ether): 0.14; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2960, 2923, 2881, 1735, 1385, 1362, 1323, 1260, 1201;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.66 – 3.60 (1 H, m,  $\text{H}_7$ ), 3.12 (1 H, dd,  $J = 2.0, 9.2$  Hz,  $\text{H}_4$ ), 2.62 (1 H, dq,  $J = 1.9, 7.4$  Hz,  $\text{H}_2$ ), 1.90 – 1.40 (16 H, m,  $\text{H}_5, \text{H}_8, \text{H}_9, \text{H}_{10}$  and  $\text{H}_{11}$ ), 1.24 (3 H, d,  $J = 7.3$  Hz,  $\text{H}_1$ ), 0.93 (3 H, t,  $J = 7.4$  Hz,  $\text{H}_6$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 169.9 ( $\text{C}_3$ ), 60.9 ( $\text{C}_4$ ), 52.7 ( $\text{C}_7$ ), 48.7 ( $\text{C}_2$ ), 32.3, 30.8, 27.1, 27.0, 26.8, 25.7, 24.6, 24.4, 13.6 ( $\text{C}_1$ ), 9.9 ( $\text{C}_6$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  224.2008,  $\text{C}_{14}\text{H}_{26}\text{ON}$  requires 224.2009.

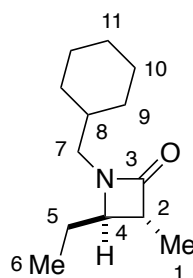
*trans*-4-ethyl-1-isobutyl-3-methylazetidin-2-one **526a**



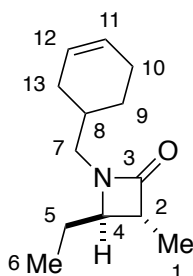
Prepared according to general procedure A using *N*-isobutylpentan-3-amine **525a** (43.0 mg, 0.3 mmol). Purification by flash column chromatography (100% petroleum ether to 20% ethyl acetate in petroleum ether) and subsequently by flash column chromatography over alumina (gradient elution:

100% petroleum ether to 20% ethyl acetate in petroleum ether) gave the title compound as a colourless oil (41.6 mg, 82%, d.r. = 10:1).  $R_f$  (20% ethyl acetate in petroleum ether): 0.14; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2961, 2929, 2873, 1748, 1474, 1407;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.14 (1 H, dd,  $J = 8.3, 14.0$  Hz,  $\text{H}_{7a}$ ), 3.10 (1 H, ddd,  $J = 2.0, 4.1, 8.8$  Hz,  $\text{H}_4$ ), 2.78 – 2.69 (2 H, m,  $\text{H}_2$  and  $\text{H}_{7b}$ ), 1.90 – 1.80 (2 H, m,  $\text{H}_{5a}$  and  $\text{H}_8$ ), 1.48 – 1.42 (1 H, m,  $\text{H}_{5b}$ ), 1.30 (3 H, d,  $J = 7.3$  Hz,  $\text{H}_1$ ), 0.96 – 0.90 (9 H, m,  $\text{H}_6$  and  $\text{H}_9$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 170.9 ( $\text{C}_3$ ), 61.7 ( $\text{C}_4$ ), 49.5 ( $\text{C}_2$ ), 47.7 ( $\text{C}_7$ ), 27.6 ( $\text{C}_8$ ), 25.2 ( $\text{C}_5$ ), 20.3 ( $\text{C}_{9a}$ ), 20.2 ( $\text{C}_{9b}$ ), 13.6 ( $\text{C}_1$ ), 9.6 ( $\text{C}_6$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  170.1536,  $\text{C}_{10}\text{H}_{20}\text{ON}$  requires 170.1539.

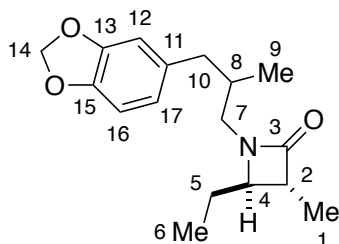
*trans*-1-(cyclohexylmethyl)-4-ethyl-3-methylazetidin-2-one **526b**



Prepared according to general procedure A using *N*-(cyclohexylmethyl)pentan-3-amine **525b** (55.0 mg, 0.3 mmol). Purification by flash column chromatography over alumina (gradient elution: 100% petroleum ether to 20% ethyl acetate in petroleum ether) and filtration over activated charcoal gave the title compound as a colourless oil (47 mg, 75%, d.r. > 20:1).  $R_f$  (10% ethyl acetate in petroleum ether): 0.15; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2962, 2924, 2852, 1739, 1449, 1406, 1364, 1287, 1262, 1212;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.18 (1 H, dd,  $J = 8.2, 14.0$  Hz,  $\text{H}_{7a}$ ), 3.08 (1 H, ddd,  $J = 1.9, 3.9, 8.8$  Hz,  $\text{H}_4$ ), 2.78 – 2.68 (2 H, m,  $\text{H}_2$  and  $\text{H}_{7b}$ ), 1.88 – 1.78 (1 H, m,  $\text{H}_{5a}$ ), 1.73 – 1.65 (5 H, m,  $\text{H}_{9a}$ ,  $\text{H}_{10a}$  and  $\text{H}_{11a}$ ), 1.58 – 1.52 (1 H, m,  $\text{H}_8$ ), 1.47 – 1.40 (1 H, m,  $\text{H}_{5b}$ ), 1.29 (3 H, d,  $J = 7.3$  Hz,  $\text{H}_1$ ), 1.25 – 1.13 (3 H, m,  $\text{H}_{10b}$  and  $\text{H}_{11b}$ ), 0.96 – 0.87 (5 H, m,  $\text{H}_6$  and  $\text{H}_{9b}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 171.1 ( $\text{C}_3$ ), 61.9 ( $\text{C}_4$ ), 49.6 ( $\text{C}_2$ ), 46.6 ( $\text{C}_7$ ), 37.0 ( $\text{C}_8$ ), 31.3 ( $\text{C}_{9a}$ ), 31.0 ( $\text{C}_{9b}$ ), 26.5 ( $\text{C}_{11}$ ), 25.9 ( $\text{C}_{10a}$ ), 25.9 ( $\text{C}_{10b}$ ), 25.3 ( $\text{C}_5$ ), 13.8 ( $\text{C}_1$ ), 9.7 ( $\text{C}_6$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  210.1854,  $\text{C}_{13}\text{H}_{24}\text{NO}$  requires 210.1852.

*1-(cyclohex-3-en-1-ylmethyl)-4-ethyl-3-methylazetidin-2-one 526c*

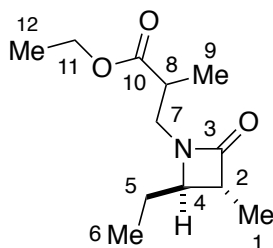
Prepared according to general procedure A using *N*-(cyclohex-3-en-1-ylmethyl)pentan-3-amine **525c** (54.4 mg, 0.3 mmol). Purification by flash column chromatography (100% petroleum ether to 20% ethyl acetate in petroleum ether) and subsequently by flash column chromatography over alumina (gradient elution: 100% petroleum ether to 20% ethyl acetate in petroleum ether) gave the title compound as a colourless oil. The product was obtained as an inseparable mixture of diastereoisomers (36.4 mg, 59%, d.r.<sub>major</sub> = 1:1). *R*<sub>f</sub> (20% ethyl acetate in petroleum ether): 0.19; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2966, 2929, 1729, 1455, 1437, 1416, 1376; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 5.69 – 5.62 (2 H, m, H<sub>11</sub> and H<sub>12</sub>), 3.27 (1 H, app td, *J* = 8.0, 14.4 Hz, H<sub>7a</sub>), 3.11 – 3.08 (1 H, m, H<sub>4</sub>), 2.86 (1 H, app dt, *J* = 6.0, 14.4 Hz, C<sub>7b</sub>), 2.72 (1 H, dq, *J* = 1.9, 7.3 Hz, H<sub>2</sub>), 2.12 – 1.97 (3 H, m, H<sub>13a</sub> and H<sub>9</sub>), 1.92 – 1.79 (2 H, m, H<sub>5a</sub> and H<sub>8</sub>), 1.77 – 1.65 (2 H, H<sub>10a</sub> and H<sub>13b</sub>), 1.51 – 1.40 (1 H, m, H<sub>5b</sub>), 1.31 – 1.23 (4 H, m, H<sub>1</sub>, H<sub>10b</sub>), 0.94 (3 H, t, *J* = 7.5 Hz, H<sub>6</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : [171.0, 170.9 (C<sub>3</sub>)], [127.2, 127.0 (C<sub>11</sub>)], [125.5, 125.4 (C<sub>12</sub>)], 61.8 (C<sub>4</sub>), [49.6, 49.5 (C<sub>2</sub>)], [45.8, 45.4 (C<sub>7</sub>)], [32.9, 32.8 (C<sub>8</sub>)], [29.6, 29.5 (C<sub>13</sub>)], [26.6, 26.3 (C<sub>10</sub>)], [25.3, 25.2 (C<sub>5</sub>)], [24.6, 24.5 (C<sub>9</sub>)], [13.7, 13.7 (C<sub>1</sub>)], [9.6, 9.6 (C<sub>6</sub>)]; *m/z* HRMS found [M + H]<sup>+</sup> 208.1702, C<sub>13</sub>H<sub>22</sub>NO requires 208.1701.

*trans-1-(2-methyl-3-(3,4-methylenedioxyphenyl)propyl)-4-ethyl-3-methylazetidin-2-one 526f*

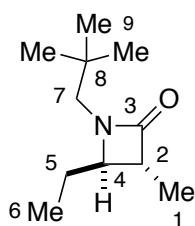
Prepared according to general procedure A using *N*-(2-methyl-3-(3,4-methylenedioxyphenyl)propyl)pentan-3-amine **525f** (78.9 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 20% ethyl acetate in petroleum ether) and subsequently by flash column chromatography over alumina (100% petroleum ether to 20% ethyl acetate in petroleum ether) gave the title compound as a colourless oil. The product was obtained as an inseparable mixture of diastereoisomers (41.7 mg, 48%, d.r.<sub>major</sub> = 1:1). *R*<sub>f</sub> (20% ethyl

acetate in petroleum ether): 0.15; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2964, 2928, 1742, 1504, 1490, 1441, 1409, 1376;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.72 (1 H, dd,  $J = 0.9, 7.9$  Hz,  $\text{H}_{16}$ ), 6.63 (1 H, d,  $J = 1.5$  Hz,  $\text{H}_{12}$ ), 6.59 (1 H, dd,  $J = 1.6, 7.9$  Hz,  $\text{H}_{17}$ ), 5.92 (2 H, s,  $\text{H}_{14}$ ), 3.27 – 3.15 (1 H, m,  $\text{H}_{7a}$ ), 3.12 – 3.05 (1 H, m,  $\text{H}_4$ ), 2.89 – 2.80 (1 H, m,  $\text{H}_{7b}$ ), 2.76 – 2.69 (1 H, m,  $\text{H}_2$ ), 2.64 – 2.56 (1 H, m,  $\text{H}_{10a}$ ), 2.36 – 2.24 (1 H, m,  $\text{H}_{10b}$ ), 2.06 – 1.91 (1 H, m,  $\text{H}_8$ ), 1.87 – 1.73 (1 H, m,  $\text{H}_{5a}$ ), 1.48 – 1.39 (1 H, m,  $\text{H}_{5b}$ ), 1.29 (3 H, dd,  $J = 0.8, 7.3$  Hz,  $\text{H}_1$ ), 0.97 – 0.91 (3 H, m,  $\text{H}_6$ ), 0.88 (3 H, d,  $J = 6.7$  Hz,  $\text{H}_9$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : [171.0, 170.9 ( $\text{C}_3$ )], 147.5 ( $\text{C}_{13}$ ), 145.8 ( $\text{C}_{15}$ ), 133.9 ( $\text{C}_{11}$ ), [121.9, 121.8 ( $\text{C}_{17}$ )], [109.4, 109.3 ( $\text{C}_{12}$ )], 108.1 ( $\text{C}_{16}$ ), 100.8 ( $\text{C}_{14}$ ), [62.2, 61.5 ( $\text{C}_4$ )], [49.6, 49.5 ( $\text{C}_2$ )], [46.3, 45.9 ( $\text{C}_7$ )], [40.9, 40.7 ( $\text{C}_{10}$ )], [34.8, 34.5 ( $\text{C}_8$ )], [24.3, 24.2 ( $\text{C}_5$ )], [17.6, 17.5 ( $\text{C}_9$ )], [13.7, 13.6 ( $\text{C}_1$ )], [9.7, 9.6 ( $\text{C}_6$ )];  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  290.1750,  $\text{C}_{17}\text{H}_{24}\text{O}_3\text{N}$  requires 290.1751.

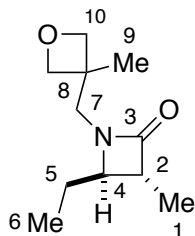
*trans*-ethyl 3-(2-ethyl-3-methyl-4-oxoazetidin-1-yl)-2-methylpropanoate **526g**



Prepared according to general procedure A using ethyl 2-methyl-3-(pentan-3-ylamino)propanoate **525g** (60.3 mg, 0.3 mmol). Purification by flash column chromatography (100% petroleum ether to 40% ethyl acetate in petroleum ether) and subsequently by flash column chromatography over alumina (gradient elution: 100% petroleum ether to 40% ethyl acetate in petroleum ether) gave the title compound as a colourless oil. The product was obtained as an inseparable mixture of diastereoisomers (40.7 mg, 60%, d.r.<sub>major</sub> = 1:1).  $R_f$  (20% ethyl acetate in petroleum ether): 0.18; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2966, 2934, 1749, 1738, 1458, 1405, 1375;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.17 – 4.10 (4 H, m,  $\text{H}_{11}$  and  $\text{H}_{11'}$ ), 3.59 (1 H, dd,  $J = 7.2, 14.0$  Hz,  $\text{H}_{7a}$ ), 3.43 (1 H, dd,  $J = 6.4, 14.0$ ,  $\text{H}_{7a'}$ ), 3.16 – 3.03 (4 H, m,  $\text{H}_{7b}$ ,  $\text{H}_{7b'}$ ,  $\text{H}_4$  and  $\text{H}_{4'}$ ), 2.77 – 2.67 (4 H, m,  $\text{H}_2$ ,  $\text{H}_2'$ ,  $\text{H}_8$  and  $\text{H}_{8'}$ ), 1.88 – 1.80 (2 H, m,  $\text{H}_{5a}$  and  $\text{H}_{5a'}$ ), 1.45 – 1.36 (2 H, m,  $\text{H}_{5b}$  and  $\text{H}_{5b'}$ ), 1.27 – 1.24 (12 H, m,  $\text{H}_{12}$ ,  $\text{H}_{12'}$ ,  $\text{H}_1$  and  $\text{H}_{1'}$ ), 1.19 – 1.14 (6 H, m,  $\text{H}_9$  and  $\text{H}_{9'}$ ), 0.92 (6 H, app t,  $J = 7.4$  Hz,  $\text{H}_6$  and  $\text{H}_{6'}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : [174.8, 174.5 ( $\text{C}_{10}$ )], [171.1, 170.9 ( $\text{C}_3$ )], [62.0, 61.8 ( $\text{C}_4$ )], 60.8 ( $\text{C}_{11}$ ), [49.7, 49.6 ( $\text{C}_2$ )], [42.8, 42.7 ( $\text{C}_7$ )], 39.1 ( $\text{C}_8$ ), [25.0, 24.8 ( $\text{C}_5$ )], [15.3, 14.7 ( $\text{C}_9$ )], 14.2 ( $\text{C}_{12}$ ), [13.5, 13.5 ( $\text{C}_1$ )], [9.4, 9.4 ( $\text{C}_6$ )];  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  228.1595,  $\text{C}_{12}\text{H}_{22}\text{O}_3\text{N}$  requires 228.1594.

*trans*-4-ethyl-3-methyl-1-neopentylazetidin-2-one **528a**

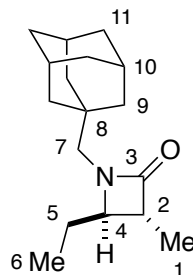
Prepared according to general procedure A using *N*-neopentylpentan-3-amine **527a** (47.2 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 20% ethyl acetate in petroleum ether) and filtration over activated charcoal gave the title compound as a colourless oil (46.7 mg, 85%, d.r. = 15:1).  $R_f$  (10% ethyl acetate in petroleum ether): 0.14; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2960, 2874, 1741, 1465, 1396, 1367, 1347, 1322, 1300, 1249, 1212;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.27 – 3.21 (2 H, m,  $\text{H}_4$  and  $\text{H}_{7a}$ ), 2.71 (1 H, dq,  $J = 7.3, 1.7$  Hz,  $\text{H}_2$ ), 2.53 (1 H, d,  $J = 14.1$  Hz,  $\text{H}_{7b}$ ), 1.93 – 1.83 (1 H, m,  $\text{H}_{5a}$ ), 1.46 – 1.37 (1 H, m,  $\text{H}_{5b}$ ), 1.31 (3 H, d,  $J = 7.3$  Hz,  $\text{H}_1$ ), 0.95 – 0.91 (12 H, m,  $\text{H}_6$  and  $\text{H}_9$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 171.5 ( $\text{C}_3$ ), 63.4 ( $\text{C}_4$ ), 51.3 ( $\text{C}_7$ ), 49.8 ( $\text{C}_2$ ), 33.5 ( $\text{C}_8$ ), 28.1 ( $\text{C}_9$ ), 24.4 ( $\text{C}_5$ ), 14.1 ( $\text{C}_1$ ), 9.4 ( $\text{C}_6$ );  $m/z$  HRMS found  $[\text{M} + \text{Na}]^+$  206.1515,  $\text{C}_{11}\text{H}_{21}\text{ONNa}$  requires 206.1515.

*trans*-4-ethyl-3-methyl-1-((3-methyloxetan-3-yl)methyl)azetidin-2-one **528b**

Prepared according to general procedure A using *N*-((3-methyloxetan-3-yl)methyl)pentan-3-amine **527b** (51.4 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 40% ethyl acetate in petroleum ether) and subsequently by flash column chromatography over alumina (gradient elution: 100% petroleum ether to 40% ethyl acetate in petroleum ether) gave the title compound as a colourless oil (40.1 mg, 67%, d.r. > 20:1).  $R_f$  (20% ethyl acetate in petroleum ether): 0.18; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2963, 2929, 2871, 1737, 1455, 1405, 1381, 1347;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.49 (2 H, dd,  $J = 2.8, 6.1$  Hz,  $\text{H}_{10a}$ ), 4.39 (2 H, dd,  $J = 4.9, 6.1$  Hz,  $\text{H}_{10b}$ ), 3.54 (1 H, d,  $J = 14.4$  Hz,  $\text{H}_{7a}$ ), 3.16 – 3.09 (2 H, m,  $\text{H}_4$  and  $\text{H}_{7b}$ ), 2.76 (1 H, dq,  $J = 1.9, 7.4$  Hz,  $\text{H}_2$ ), 1.94 – 1.84 (1 H, m,  $\text{H}_{5a}$ ), 1.51 – 1.40 (1 H, m,  $\text{H}_{5b}$ ), 1.32 – 1.30 (6 H, m,  $\text{H}_1$  and  $\text{H}_9$ ), 0.95 (3 H, t,  $J = 7.4$  Hz,  $\text{H}_6$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 171.3 ( $\text{C}_3$ ), 80.9 ( $\text{C}_{10a}$ ), 80.8 ( $\text{C}_{10b}$ ), 62.4 ( $\text{C}_4$ ), 49.9 ( $\text{C}_2$ ), 47.2 ( $\text{C}_7$ ), 40.3 ( $\text{C}_8$ ), 24.8 ( $\text{C}_5$ ), 22.2 ( $\text{C}_6$ ), 13.8 ( $\text{C}_1$ ), 9.3 ( $\text{C}_6$ );  $m/z$  HRMS

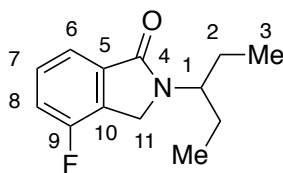
found  $[M+H]^+$  198.1483,  $C_{11}H_{20}O_2N$  requires 198.1489.

*trans*-1-(adamantan-1-ylmethyl)-4-ethyl-3-methylazetidin-2-one **528c**



Prepared according to general procedure A using *N*-(adamantan-1-ylmethyl)pentan-3-amine **527c** (63 mg, 0.3 mmol). Purification by flash column chromatography over alumina (gradient elution: 100% petroleum ether to 15% ethyl acetate petroleum ether) provided the title compound as a colourless oil (67 mg, 80%, d.r. = 12:1).  $R_f$  (20% ethyl acetate in petroleum ether): 0.25; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2898, 2846, 1741, 1451, 1401, 1366, 1088;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.19 (1H, ddd,  $J$  = 2.0, 3.4, 9.0 Hz,  $H_4$ ), 3.10 (1H, d,  $J$  = 14.3 Hz,  $H_{7a}$ ), 2.70 (1H, qd,  $J$  = 1.7, 7.4 Hz,  $H_2$ ), 2.40 (1H, d,  $J$  = 14.3 Hz,  $H_{7b}$ ), 1.96 (3H, m,  $H_{10}$ ), 1.86 (1H, m,  $H_{5a}$ ), 1.70 (3H, m,  $H_{9a}$ ), 1.61 (3H, m,  $H_{9b}$ ), 1.51 (6H, m,  $H_{11}$ ), 1.39 (1H, m,  $H_5$ ), 1.32 (3H, d,  $J$  = 7.4 Hz,  $H_1$ ), 0.93 (3H, t,  $J$  = 7.5 Hz,  $H_6$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 171.6 ( $C_3$ ), 63.8 ( $C_4$ ), 51.8 ( $C_7$ ), 49.8 ( $C_2$ ), 41.0 ( $C_9$ ), 36.9 ( $C_{11}$ ), 35.3 ( $C_8$ ), 28.3 ( $C_{10}$ ), 24.4 ( $C_5$ ), 14.2 ( $C_1$ ), 9.4 ( $C_6$ );  $m/z$  HRMS found  $[M + H]^+$  262.2165,  $C_{17}H_{28}ON$  requires 262.2165.

4-fluoro-2-(pentan-3-yl)isoindolin-1-one **530a**

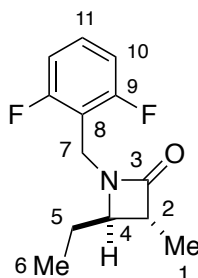


Prepared according to general procedure A using *N*-(2-fluorobenzyl)pentan-3-amine **529a** (58.6 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 20% ethyl acetate in petroleum ether) gave the title compound as colourless needles (31.3 mg, 47%).  $R_f$  (20% ethyl acetate in petroleum ether): 0.41; m.p. 54 – 60 °C; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2964, 2929, 2872, 1763, 1677, 1601, 1485, 1458, 1413, 1365, 1336, 1295, 1278, 1247, 1216;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.66 (1 H, d,  $J$  = 7.5 Hz,  $H_6$ ), 7.48 – 7.44 (1 H, m,  $H_7$ ), 7.23 – 7.19 (1 H, m,  $H_8$ ), 4.29 (2 H, s,  $H_{11}$ ), 4.22 (1 H, spt,  $J$  = 4.9 Hz,  $H_1$ ), 1.76 – 1.68 (2 H, m,  $H_{2a}$ ), 1.64 – 1.55 (2 H, m,  $H_{2b}$ ), 0.88 (6 H, t,  $J$  = 7.4 Hz,  $H_3$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 168.3 ( $C_4$ ), 157.8 (d,  $^1J_{C-F}$  = 246.9

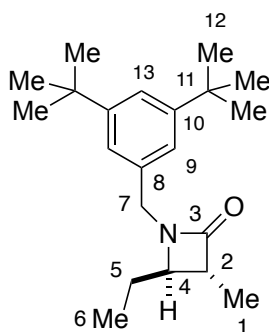


Hz, C<sub>9</sub>), 136.4 (d,  $^3J_{\text{C-F}} = 4.3$  Hz, C<sub>5</sub>), 130.3 (d,  $^3J_{\text{C-F}} = 6.3$  Hz, C<sub>7</sub>), 127.3 (d,  $^2J_{\text{C-F}} = 18.7$  Hz, C<sub>10</sub>), 119.9 (d,  $^4J_{\text{C-F}} = 3.4$  Hz, C<sub>6</sub>), 117.9 (d,  $^2J_{\text{C-F}} = 19.6$  Hz, C<sub>8</sub>), 54.8 (C<sub>1</sub>), 42.2 (C<sub>11</sub>), 26.6 (C<sub>2</sub>), 11.0 (C<sub>3</sub>);  $^{19}\text{F}\{^1\text{H}\}$  NMR (377 MHz, CDCl<sub>3</sub>)  $\delta$ : -121.7; m/z HRMS found  $[\text{M} + \text{Na}]^+$  244.1106, C<sub>13</sub>H<sub>16</sub>FONa requires 244.1108.

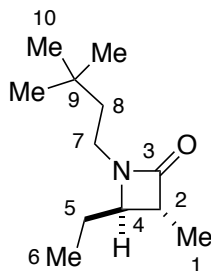
*trans*-1-(2,6-difluorobenzyl)-4-ethyl-3-methylazetidin-2-one **530d**



To an oven-dried 100 mL round-bottomed flask equipped with reflux condenser and a large oval stirrer bar was added Pd(OPiv)<sub>2</sub> (0.093 g, 0.3 mmol), AgOPiv (1.89 g, 9.0 mmol), Xantphos (0.17 g, 0.3 mmol) and 1,4-benzoquinone (0.66 g, 6.0 mmol). The flask was charged with anhydrous toluene (30 mL) and *N*-(2,6-difluorobenzyl)pentan-3-amine **529d** (0.640 g, 3.0 mmol) and the condenser attached and the joint sealed with Teflon tape. A new septa was placed on top of the condenser and further sealed with Teflon tape. A balloon of CO was placed on top and the system evacuated and backfilled (3 cycles). The flask was then immersed into a preheated oil bath at 80 °C so as the solvent level and oil level matched and stirred at 500 rpm for 18 hours. The flask was removed and cooled to room temperature and the contents were filtered over celite and washed with ethyl acetate (20 mL). The organics were combined and removed *in vacuo* and the residue purified by flash column chromatography (gradient elution: 100% petroleum ether to 20% ethyl acetate in petroleum ether) and subsequently by flash column chromatography over alumina (gradient elution: 100% petroleum ether to 20% ethyl acetate in petroleum ether) to afford the title compound as a colourless oil (0.557 g, 78%, d.r. > 20:1). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.11; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2966, 2931, 2878, 1744, 1625, 1593, 1563, 1471, 1398, 1367, 1318, 1267, 1235;  $^1\text{H}$  NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.31 – 7.23 (1 H, m, H<sub>11</sub>), 6.90 (2 H, t,  $J = 7.6$  Hz, H<sub>10</sub>), 4.67 (1 H, d,  $J = 14.8$  Hz, H<sub>7a</sub>), 4.22 (1 H, d,  $J = 14.7$  Hz, H<sub>7b</sub>), 2.97 – 2.93 (1 H, m, H<sub>4</sub>), 2.74 (1 H, dq,  $J = 7.4, 1.7$  Hz, H<sub>2</sub>), 1.82 – 1.72 (1 H, m, H<sub>5a</sub>), 1.44 – 1.33 (1 H, m, H<sub>5b</sub>), 1.21 (3 H, d,  $J = 7.4$  Hz, H<sub>1</sub>), 0.87 (3 H, t,  $J = 7.4$  Hz, H<sub>6</sub>);  $^{13}\text{C}$  (100 MHz, CDCl<sub>3</sub>)  $\delta$  170.3 (C<sub>3</sub>), 161.6 (dd,  $^1J_{\text{C-F}} = 249.7$ ,  $^3J_{\text{C-F}} = 8.0$  Hz, C<sub>9</sub>), 130.0 (t,  $^3J_{\text{C-F}} = 10.3$  Hz, C<sub>11</sub>), 111.8 (t,  $^2J_{\text{C-F}} = 19.7$  Hz, C<sub>8</sub>), 111.6 (m, C<sub>10</sub>), 61.5 (C<sub>4</sub>), 49.8 (C<sub>2</sub>), 31.8 (t,  $^3J_{\text{C-F}} = 4.0$  Hz, C<sub>7</sub>), 25.1 (C<sub>5</sub>), 13.3 (C<sub>1</sub>), 9.4 (C<sub>6</sub>);  $^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$ : -115.1; m/z HRMS found  $[\text{M} + \text{Na}]^+$  262.1010, C<sub>13</sub>H<sub>15</sub>F<sub>2</sub>NONa requires 262.1014.

*trans*-1-(3,5-di-*tert*-butylbenzyl)-4-ethyl-3-methylazetidin-2-one **530g**

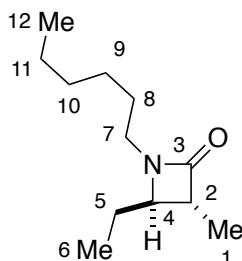
Prepared according to general procedure A using *N*-(3,5-di-*tert*-butylbenzyl)pentan-3-amine **529g** (86.9 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 20% ethyl acetate in petroleum ether) gave the title compound as a colourless oil (35.7 mg, 38%).  $R_f$  (10% ethyl acetate in petroleum ether): 0.14; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2961, 2870, 1735, 1702, 1600, 1480, 1456, 1394, 1363, 1249, 1199, 1166, 1027;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.33 (1 H, app t,  $J = 1.7$  Hz,  $\text{H}_{13}$ ), 7.06 (2 H, d,  $J = 1.4$  Hz,  $\text{H}_9$ ), 4.68 (1 H, d,  $J = 15.1$  Hz,  $\text{H}_{7a}$ ), 4.03 (1 H, d,  $J = 15.1$  Hz,  $\text{H}_{7b}$ ), 2.98 (1 H, ddd,  $J = 1.9, 4.3, 6.3$  Hz,  $\text{H}_4$ ), 2.79 (1 H, dq,  $J = 1.6, 7.5$  Hz,  $\text{H}_2$ ), 1.74 – 1.64 (1 H, m,  $\text{H}_{5a}$ ), 1.43 – 1.36 (1 H, m,  $\text{H}_{5b}$ ), 1.31 (18 H, s,  $\text{H}_{12}$ ), 1.28 (3 H, d,  $J = 7.2$  Hz,  $\text{H}_1$ ), 0.86 (3 H, t,  $J = 7.4$  Hz,  $\text{H}_6$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 171.2 ( $\text{C}_3$ ), 151.3 ( $\text{C}_{10}$ ), 135.3 ( $\text{C}_8$ ), 122.41 ( $\text{C}_9$ ), 121.5 ( $\text{C}_{13}$ ), 61.0 ( $\text{C}_4$ ), 49.6 ( $\text{C}_2$ ), 44.9 ( $\text{C}_7$ ), 34.9 ( $\text{C}_{11}$ ), 31.6 ( $\text{C}_{12}$ ), 25.3 ( $\text{C}_5$ ), 13.4 ( $\text{C}_1$ ), 9.7 ( $\text{C}_6$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  316.2634,  $\text{C}_{21}\text{H}_{34}\text{ON}$  requires 316.2635.

*trans*-1-(3,3-dimethylbutyl)-4-ethyl-3-methylazetidin-2-one **534a**

Prepared according to general procedure A using *N*-(3,3-dimethylbutyl)pentan-3-amine **533a** (51.4 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 30% ethyl acetate in petroleum ether) and filtration over activated charcoal gave the title compound as a colourless oil (31.8 mg, 54%, d.r. 8:1).  $R_f$  (20% ethyl acetate in petroleum ether): 0.23; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2960, 2869, 1746, 1459, 1408, 1366;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.38 (1 H, ddd,  $J = 6.2, 11.2, 13.8$  Hz,  $\text{H}_{7a}$ ), 3.09 (1 H, ddd,  $J = 1.9, 4.2, 6.2$  Hz,  $\text{H}_4$ ), 2.95 (1 H, ddd,  $J = 5.6, 10.5, 13.7$  Hz,  $\text{H}_{7b}$ ), 2.68 (1 H, dq,  $J = 1.4, 7.4$  Hz,  $\text{H}_2$ ), 1.86 – 1.76 (1 H, m,  $\text{H}_{5a}$ ), 1.49 – 1.38 (3 H, m,  $\text{H}_{5b}$  and  $\text{H}_8$ ), 1.26 (3 H, d,  $J = 7.4$  Hz,  $\text{H}_1$ ), 0.95 (3 H, t,  $J = 7.6$  Hz,  $\text{H}_6$ ), 0.91 (9 H, s,  $\text{H}_{10}$ );  $^{13}\text{C}$

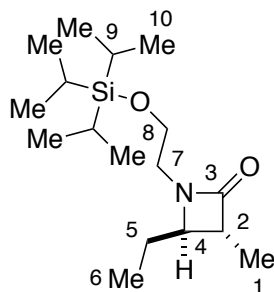
NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 170.6 (C<sub>3</sub>), 61.1 (C<sub>4</sub>), 49.4 (C<sub>2</sub>), 41.3 (C<sub>8</sub>), 36.8 (C<sub>7</sub>), 29.8 (C<sub>9</sub>), 29.4 (C<sub>10</sub>), 25.6 (C<sub>5</sub>), 13.3 (C<sub>1</sub>), 9.8 (C<sub>6</sub>); m/z HRMS found [M + H]<sup>+</sup> 198.1849, C<sub>12</sub>H<sub>24</sub>ON requires 198.1852.

*trans*-4-ethyl-1-hexyl-3-methylazetidin-2-one **534b**



Prepared according to general procedure A using *N*-(pentan-3-yl)hexan-1-amine **533b** (51.4 mg, 0.3 mmol), Pd(OPiv)<sub>2</sub> (9.3 mg, 0.03 mmol), Xantphos (17.4 mg, 0.03 mmol), 1,4-benzoquinone (65 mg, 0.6 mmol) and AgOPiv (188 mg, 0.9 mmol) in toluene (3 mL) at 80 °C for 18 hours. Flash column chromatography (gradient elution: 100% petroleum ether to 10% ethyl acetate in petroleum ether) provided the title compound as colourless oil (24 mg, 40%, d.r. >20:1). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2959, 2927, 2958, 1740, 1456, 1404, 1370. R<sub>f</sub> (20% ethyl acetate in petroleum ether): 0.32; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 3.31 (1H, dt, *J* = 14.0, 7.6 Hz, H<sub>7a</sub>), 3.07 (1H, ddd, *J* = 1.8, 4.0 8.6 Hz, H<sub>4</sub>), 2.95 (1H, dt, *J* = 7.6, 14.0 Hz, H<sub>7b</sub>), 2.69 (1H, qd, *J* = 1.8, 7.3 Hz, H<sub>2</sub>), 1.81 (1H, m, H<sub>5a</sub>), 1.55 – 1.39 (3H, m, H<sub>5b</sub> and H<sub>8</sub>), 1.27 (9H, m, H<sub>1</sub>, H<sub>9</sub>, H<sub>10</sub> and H<sub>11</sub>), 0.94 (3H, t, *J* = 7.5 Hz, H<sub>6</sub>), 0.87 (3H, t, *J* = 6.2 Hz, H<sub>12</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 170.6 (C<sub>3</sub>), 61.3 (C<sub>4</sub>), 49.4 (C<sub>2</sub>), 40.2 (C<sub>7</sub>), 31.4 (C<sub>10</sub>), 28.1 (C<sub>8</sub>), 26.7 (C<sub>9</sub>), 25.5 (C<sub>5</sub>), 22.6 (C<sub>11</sub>), 14.0 (C<sub>1</sub>), 13.5 (C<sub>12</sub>), 9.7 (C<sub>6</sub>); m/z HRMS found [M + H]<sup>+</sup> 198.1848, C<sub>12</sub>H<sub>24</sub>ON requires 198.1852.

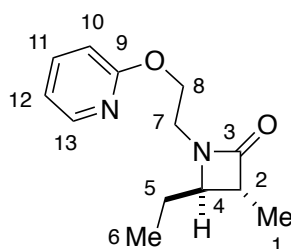
*trans*-4-ethyl-3-methyl-1-(2-((triisopropylsilyl)oxy)ethyl)azetidin-2-one **538a**



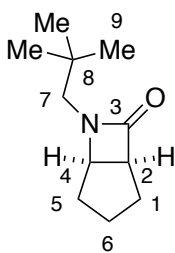
Prepared according to general procedure A using *N*-(2-((triisopropylsilyl)oxy)ethyl)pentan-3-amine **537a** (86.3 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 10% ethyl acetate in petroleum ether) and subsequently by flash column chromatography over alumina (gradient elution: 100% petroleum ether to 10% ethyl acetate in

petroleum ether) gave the title compound as a colourless oil (73.4 mg, 78%, d.r. = 9:1).  $R_f$  (10% ethyl acetate in petroleum ether): 0.29; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2942, 2866, 1748, 1463, 1401;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.85 – 3.75 (2 H, m,  $\text{H}_8$ ), 3.52 (1 H, app dt,  $J = 4.8, 14.3$  Hz,  $\text{H}_{7a}$ ), 3.25 (1 H, ddd,  $J = 2.0, 3.8, 8.9$  Hz,  $\text{H}_4$ ), 3.08 – 3.01 (1 H, m,  $\text{H}_{7b}$ ), 2.71 (1 H, dq,  $J = 1.5, 7.3$  Hz,  $\text{H}_2$ ), 1.96 – 1.86 (1 H, m,  $\text{H}_{5a}$ ), 1.49 – 1.38 (1 H, m,  $\text{H}_{5b}$ ), 1.28 (3 H, d,  $J = 7.3$  Hz,  $\text{H}_1$ ), 1.08 – 1.04 (21 H, m,  $\text{H}_9$  and  $\text{H}_{10}$ ), 0.93 (3 H, t,  $J = 7.4$  Hz,  $\text{H}_6$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 170.8 ( $\text{C}_3$ ), 62.4 ( $\text{C}_4$ ), 62.2 ( $\text{C}_8$ ), 49.8 ( $\text{C}_2$ ), 42.2 ( $\text{C}_7$ ), 25.1 ( $\text{C}_5$ ), 18.0 ( $\text{C}_{10}$ ), 13.3 ( $\text{C}_1$ ), 11.9 ( $\text{C}_9$ ), 9.5 ( $\text{C}_6$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  314.2509,  $\text{C}_{17}\text{H}_{36}\text{O}_2\text{NSi}$  requires 314.2510.

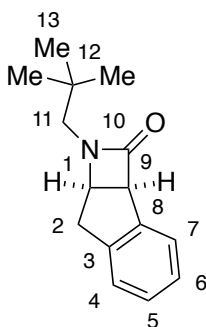
*trans*-4-ethyl-3-methyl-1-(2-(pyridin-2-yloxy)ethyl)azetidin-2-one **538b**



Prepared according to general procedure A using *N*-(2-(pyridin-2-yloxy)ethyl)pentan-3-amine **537b** (62.5 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 50% ethyl acetate in petroleum ether) gave the title compound as colourless oil (22.3 mg, 32%, d.r. 14:1).  $R_f$  (30% ethyl acetate in petroleum ether): 0.10; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2964, 2930, 2876, 1739, 1657, 1595, 1571, 1475, 1432, 1404, 1375, 1310, 1274, 1247, 1208, 1143, 1114, 1049, 1023;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.15 (1 H, dd,  $J = 1.3, 5.0$  Hz,  $\text{H}_{13}$ ), 7.59 (1 H, dt,  $J = 1.9, 8.7$  Hz,  $\text{H}_{11}$ ), 6.92 – 6.88 (1 H, m,  $\text{H}_{12}$ ), 6.74 (1 H, d,  $J = 8.4$  Hz,  $\text{H}_{10}$ ), 4.51 – 4.38 (2 H, m,  $\text{H}_8$ ), 3.77 (1 H, ddd,  $J = 4.7, 6.4, 10.8$  Hz,  $\text{H}_{7a}$ ), 3.40 (1 H, ddd,  $J = 4.6, 6.5, 11.2$  Hz,  $\text{H}_{7b}$ ), 3.22 (1 H, ddd,  $J = 2.1, 4.0, 6.0$  Hz,  $\text{H}_4$ ), 2.75 (1 H, dq,  $J = 1.5, 7.2$  Hz,  $\text{H}_2$ ), 1.92 – 1.86 (1 H, m,  $\text{H}_{5a}$ ), 1.53 – 1.46 (1 H, m,  $\text{H}_{5b}$ ), 1.26 (3 H, d,  $J = 7.3$  Hz,  $\text{H}_1$ ), 0.96 (3 H, t,  $J = 7.4$  Hz,  $\text{H}_6$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 171.1 ( $\text{C}_3$ ), 163.3 ( $\text{C}_9$ ), 146.9 ( $\text{C}_{13}$ ), 138.9 ( $\text{C}_{11}$ ), 117.2 ( $\text{C}_{12}$ ), 111.2 ( $\text{C}_{10}$ ), 63.6 ( $\text{C}_8$ ), 62.3 ( $\text{C}_4$ ), 49.9 ( $\text{C}_2$ ), 39.6 ( $\text{C}_7$ ), 25.4 ( $\text{C}_5$ ), 13.4 ( $\text{C}_1$ ), 9.7 ( $\text{C}_6$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  235.1442,  $\text{C}_{13}\text{H}_{19}\text{O}_2\text{N}_2$  requires 235.1441.

*cis*-6-neopentyl-6-azabicyclo[3.2.0]heptan-7-one **540a**

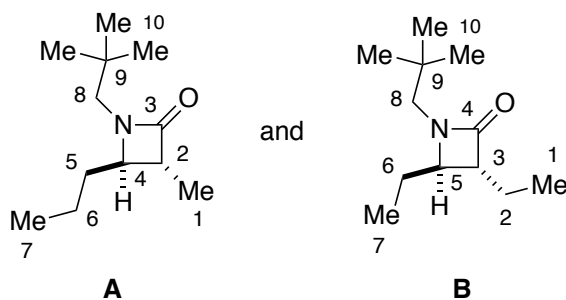
Prepared according to general procedure A using *N*-neopentylcyclopentanamine **539a** (46.6 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 20% ethyl acetate in petroleum ether) and filtration over activated charcoal gave the title compound as a white solid (35.9 mg, 66%).  $R_f$  (10% ethyl acetate in petroleum ether): 0.19; m.p. 44 – 46 °C; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2952, 2861, 1730, 1474, 1462, 1431, 1402, 1389, 1362, 1248, 1338, 1321, 1301, 1291, 1243, 1214;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.07 (1 H, t,  $J$  = 4.0 Hz,  $\text{H}_4$ ), 3.50 (1 H, dd,  $J$  = 3.4, 7.5 Hz,  $\text{H}_2$ ), 3.21 (1 H, d,  $J$  = 13.8 Hz,  $\text{H}_{7a}$ ), 2.42 (1 H, d,  $J$  = 13.8 Hz,  $\text{H}_{7b}$ ), 2.04 – 1.94 (2 H, m,  $\text{H}_{5a}$  and  $\text{H}_{1a}$ ), 1.84 – 1.78 (1 H, m,  $\text{H}_{6a}$ ), 1.58 – 1.23 (3 H, m,  $\text{H}_{1b}$ ,  $\text{H}_{5b}$  and  $\text{H}_{6b}$ ), 0.94 (9 H, s,  $\text{H}_9$ );  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$ : 170.8 ( $\text{C}_3$ ), 59.9 ( $\text{C}_4$ ), 55.1 ( $\text{C}_2$ ), 51.3 ( $\text{C}_7$ ), 33.1 ( $\text{C}_8$ ), 28.1 ( $\text{C}_9$ ), 26.4 ( $\text{C}_5$ ), 25.1 ( $\text{C}_1$ ), 22.7 ( $\text{C}_6$ ); m/z HRMS found  $[\text{M} + \text{Na}]^+$  204.1359,  $\text{C}_{11}\text{H}_{19}\text{NONa}$  requires 204.1359.

*cis*-1-neopentyl-1,2a,7,7a-tetrahydro-2*H*-indeno[2,1-*b*]azet-2-one **540b**

Prepared according to general procedure A using *N*-neopentyl-2-indanamine **539b** (61 mg, 0.3 mmol). Purification by flash column chromatography over alumina (gradient elution: 100% petroleum ether to 20% ethyl acetate petroleum ether) gave the title compound as a white crystalline solid (35.7 mg, 52%).  $R_f$  (20% ethyl acetate in petroleum ether): 0.29; m.p. 122 – 124 °C; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2955, 2905, 2865, 1743, 1730, 1690, 1602, 1475, 1459, 1432, 1398, 1334, 1322, 1296, 1268, 1244, 1230, 1213, 1163, 1103, 1063, 1031, 1011;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.44 – 7.42 (1 H, m,  $\text{H}_7$ ), 7.26 – 7.22 (3 H, m,  $\text{H}_4$ ,  $\text{H}_5$  and  $\text{H}_6$ ), 4.62 (1 H, d,  $J$  = 3.7 Hz,  $\text{H}_9$ ), 4.52 (1 H, dd,  $J$  = 4.0, 6.3 Hz,  $\text{H}_2$ ), 3.19 – 3.14 (2 H, m,  $\text{H}_{2a}$  and  $\text{H}_{11a}$ ), 3.01 (1 H, dd,  $J$  = 6.6, 17.5 Hz,  $\text{H}_{2b}$ ), 2.67 (1 H, d,  $J$  = 14.2 Hz,  $\text{H}_{11b}$ ), 0.99 (9 H, s,  $\text{H}_{13}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 169.4 ( $\text{C}_{10}$ ), 141.7 ( $\text{C}_3$ ),

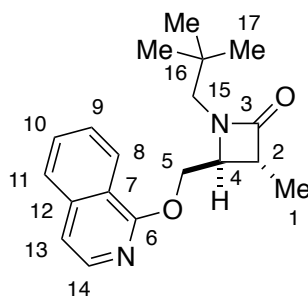
137.4 (C<sub>8</sub>), 127.9 (C<sub>5</sub>), 127.3 (C<sub>6</sub>), 126.2 (C<sub>4</sub>), 125.2 (C<sub>7</sub>), 62.8 (C<sub>9</sub>), 57.6 (C<sub>1</sub>), 51.2 (C<sub>11</sub>), 33.1 (C<sub>12</sub>), 32.2 (C<sub>2</sub>), 28.1 (C<sub>13</sub>); m/z HRMS found [M + H]<sup>+</sup> 230.1540, C<sub>15</sub>H<sub>20</sub>ON requires 230.1545.

*trans*-3-methyl-1-neopentyl-4-propylazetidin-2-one **542a** (A) and *trans*-3,4-diethyl-1-neopentylazetidin-2-one **542a'** (B)



Prepared according to general procedure A using *N*-neopentylhexan-3-amine **541a** (51.4 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 20% ethyl acetate in petroleum ether) gave the title compounds, an inseparable mixture of isomers (1:1 by crude <sup>1</sup>H NMR), as a colourless oil (50 mg, 83%, d.r. >20:1). IR ν<sub>max</sub>/cm<sup>-1</sup> (film): 2960, 2933, 2873, 1746, 1461, 1396, 1367, 1318, 1250, 1210, 1121. R<sub>f</sub> (20% ethyl acetate in petroleum ether): 0.30; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.30 – 3.21 (4 H, m, HA<sub>8a</sub>, HB<sub>8a</sub>, HA<sub>4</sub> and HB<sub>5</sub>), 2.71 – 2.61 (2 H, m, HA<sub>2</sub> and HB<sub>3</sub>), 2.51 (2 H, t, *J* = 14.3 Hz, HA<sub>8b</sub> and HB<sub>8b</sub>), 1.91 – 1.74 (3 H, m, HA<sub>5a</sub>, HB<sub>6a</sub>, HB<sub>2a</sub>), 1.69 – 1.58 (1 H, HB<sub>2b</sub>), 1.41 – 1.28 (7 H, m, HA<sub>5b</sub>, HB<sub>6b</sub>, HA<sub>6</sub> and HA<sub>7</sub>), 1.00 (3 H, t, *J* = 7.5 Hz, HB<sub>1</sub>), 0.96 – 0.89 (24 H, m, HA<sub>10</sub>, HB<sub>10</sub>, HA<sub>1</sub> and HB<sub>7</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 171.5 (CA<sub>3</sub>), 170.8 (CB<sub>4</sub>), 62.1 (CA<sub>4</sub>), 61.0 (CB<sub>5</sub>), 56.7 (CB<sub>3</sub>), 51.2 (CA<sub>8</sub> and CB<sub>8</sub>), 50.4 (CA<sub>2</sub>), 33.7 (CA<sub>5</sub>), 33.4 (CA<sub>9</sub> and CB<sub>9</sub>), 28.1 (CA<sub>10</sub> and CB<sub>10</sub>), 24.2 (CB<sub>6</sub>), 22.1 (CB<sub>2</sub>), 18.9 (CA<sub>6</sub>), 14.2 (CA<sub>1</sub>), 14.0 (CA<sub>7</sub>), 11.9 (CB<sub>1</sub>), 9.5 (CB<sub>7</sub>); m/z HRMS found [M + H]<sup>+</sup> 198.1853, C<sub>12</sub>H<sub>24</sub>ON requires 198.1858.

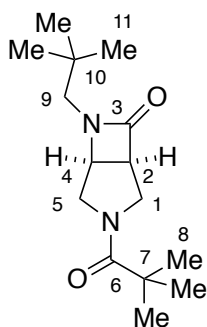
*trans*-4-((isoquinolin-1-yl)oxy)methyl-3-methyl-1-neopentylazetidin-2-one **544g**



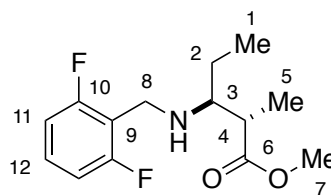
Prepared according to general procedure A using 1-(isoquinolin-1-yl)oxy)-*N*-neopentylbutan-2-amine **543g** (85.9 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100%

petroleum ether to 20% ethyl acetate in petroleum ether) and subsequently by flash column chromatography over alumina (gradient elution: 100% petroleum ether to 20% ethyl acetate in petroleum ether) gave the title compound as a colourless oil (58.8 mg, 63%, d.r. > 20:1).  $R_f$  (20% ethyl acetate in petroleum ether): 0.14; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 3057, 2959, 1748, 1628, 1592, 1571, 1500, 1455, 1406, 1367, 1326, 1305;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.18 (1 H, dd,  $J = 1.0, 8.3$  Hz,  $\text{H}_8$ ), 7.97 (1 H, d,  $J = 5.90$  Hz,  $\text{H}_{14}$ ), 7.75 (1 H, d,  $J = 8.2$  Hz,  $\text{H}_{11}$ ), 7.69 – 7.66 (1 H, m,  $\text{H}_9$ ), 7.57 – 7.54 (1 H, m,  $\text{H}_{10}$ ), 7.26 – 7.25 (1 H, m,  $\text{H}_{13}$ ), 4.80 (1 H, dd,  $J = 3.5, 11.6$  Hz,  $\text{H}_{5a}$ ), 4.66 (1 H, dd,  $J = 5.0, 11.6$  Hz,  $\text{H}_{5b}$ ), 3.84 – 3.82 (1 H, m,  $\text{H}_4$ ), 3.35 (1 H, d,  $J = 14.2$  Hz,  $\text{H}_{15a}$ ), 3.18 (1 H, dq,  $J = 2.0, 7.4$  Hz,  $\text{H}_2$ ), 2.77 (1 H, d,  $J = 14.2$  Hz,  $\text{H}_{15b}$ ), 1.44 (3 H, d,  $J = 7.0$  Hz,  $\text{H}_1$ ), 0.98 (9 H, s,  $\text{H}_{17}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 171.4 ( $\text{C}_3$ ), 159.7 ( $\text{C}_6$ ), 139.4 ( $\text{C}_{14}$ ), 138.0 ( $\text{C}_7$ ), 130.7 ( $\text{C}_9$ ), 127.0 ( $\text{C}_{10}$ ), 126.3 ( $\text{C}_{11}$ ), 123.8 ( $\text{C}_8$ ), 119.5 ( $\text{C}_{12}$ ), 115.6 ( $\text{C}_{13}$ ), 64.7 ( $\text{C}_5$ ), 60.4 ( $\text{C}_4$ ), 52.3 ( $\text{C}_{15}$ ), 47.5 ( $\text{C}_2$ ), 33.5 ( $\text{C}_{16}$ ), 28.0 ( $\text{C}_{16}$ ), 13.6 ( $\text{C}_1$ ); m/z HRMS found  $[\text{M} + \text{H}]^+$  313.1912,  $\text{C}_{19}\text{H}_{25}\text{O}_2\text{N}_2$  requires 313.1911.

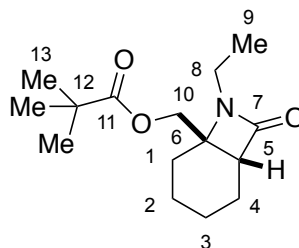
*cis*-6-neopentyl-3-pivaloyl-3,6-diazabicyclo[3.2.0]heptan-7-one **544i**



Prepared according to general procedure A using 1-pivaloyl-3-(neopentylamino)pyrrolidine **543i** (72.1 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 30% ethyl acetate in petroleum ether to 50% ethyl acetate in petroleum ether) and subsequently by flash column chromatography over alumina (gradient elution: 30% ethyl acetate in petroleum ether to 50% ethyl acetate in petroleum ether) gave the title compound as a white solid (40.4 mg, 51%).  $R_f$  (50% ethyl acetate in petroleum ether): 0.15; m.p. 148 – 150 °C; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2958, 2873, 1731, 1618, 1475, 1408, 1364, 1347;  $^1\text{H}$  NMR (400 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 4.34 (1 H, d,  $J = 13.2$  Hz,  $\text{H}_{5a}$ ), 4.00 (1 H, d,  $J = 11.8$  Hz,  $\text{H}_{1a}$ ), 3.30 (1 H, t,  $J = 3.9$  Hz,  $\text{H}_4$ ), 3.08 (1 H, d,  $J = 14.2$  Hz,  $\text{H}_{9a}$ ), 2.90 (1 H, dd,  $J = 4.2, 6.4$  Hz,  $\text{H}_2$ ), 2.41 (1 H, dd,  $J = 6.4, 11.7$  Hz,  $\text{H}_{1b}$ ), 2.30 (1 H, dd,  $J = 3.9, 13.5$  Hz,  $\text{H}_{5b}$ ), 2.13 (1 H, d,  $J = 14.3$  Hz,  $\text{H}_{9b}$ ), 1.18 (9 H, s,  $\text{H}_8$ ), 0.73 (9 H, s,  $\text{H}_{11}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 177.0 ( $\text{C}_6$ ), 167.4 ( $\text{C}_3$ ), 56.3 ( $\text{C}_4$ ), 55.1 ( $\text{C}_2$ ), 52.2 ( $\text{C}_9$ ), 45.7 ( $\text{C}_5$ ), 45.6 ( $\text{C}_1$ ), 38.9 ( $\text{C}_7$ ), 32.9 ( $\text{C}_{10}$ ), 27.8 ( $\text{C}_8$  and  $\text{C}_{11}$ ); m/z HRMS found  $[\text{M} + \text{H}]^+$  267.2066,  $\text{C}_{15}\text{H}_{27}\text{O}_2\text{N}_2$  requires 267.2067.

*methyl ((2,3-anti)-3-((2,6-difluorobenzyl)amino)-2-methylpentanoate) 549*

A solution of 1-(2,6-difluorobenzyl)-4-ethyl-3-methylazetidin-2-one **530d** (64.4 mg, 0.27 mmol) in methanolic HCl (*ca.* 1.25 M) (2 mL) was heated at 60 °C for 24 hours under N<sub>2</sub>. The reaction mixture was then cooled to room temperature and the solvent removed *in vacuo*. The residue was dissolved in dichloromethane (10 mL) and washed with saturated aqueous NaHCO<sub>3</sub> (10 mL). The aqueous was re-extracted using dichloromethane (3 x 10 mL) and the combined organics were dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed *in vacuo* to give the title compound as a colourless oil (65.8 mg, 91%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2965, 2878, 1732, 1625, 1592, 1469, 1435, 1379, 1347; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.21 – 7.15 (1 H, m, H<sub>12</sub>), 6.87 – 6.83 (2 H, m, H<sub>11</sub>), 3.86 – 3.80 (2 H, m, H<sub>8</sub>), 3.64 (3 H, s, H<sub>7</sub>), 2.72 – 2.69 (1 H, m, H<sub>3</sub>), 2.67 – 2.61 (1 H, m, H<sub>4</sub>), 1.57 – 1.45 (1 H, m, H<sub>2a</sub>), 1.41 – 1.32 (1 H, m, H<sub>2b</sub>), 1.09 (3 H, d,  $J = 7.0$  Hz, H<sub>5</sub>), 0.86 (3 H, t,  $J = 7.6$  Hz, H<sub>1</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 176.1 (C<sub>6</sub>), 161.8 (dd,  $^1J_{\text{C-F}} = 246.8$  Hz,  $^3J_{\text{C-F}} = 8.2$  Hz, C<sub>10</sub>), 128.7 (t,  $^3J_{\text{C-F}} = 10.4$  Hz, C<sub>12</sub>), 116.2 (t,  $^2J_{\text{C-F}} = 20.0$  Hz, C<sub>9</sub>), 111.3 – 111.0 (m, C<sub>11</sub>), 60.4 (C<sub>3</sub>), 51.5 (C<sub>7</sub>), 42.8 (C<sub>4</sub>), 38.6 (t,  $^3J_{\text{C-F}} = 2.9$  Hz, C<sub>8</sub>), 23.4 (C<sub>2</sub>), 12.8 (C<sub>5</sub>), 9.5 (C<sub>1</sub>); *m/z* HRMS found [M+H]<sup>+</sup> 272.1450, C<sub>14</sub>H<sub>20</sub>O<sub>2</sub>NF<sub>2</sub> requires 272.1457.

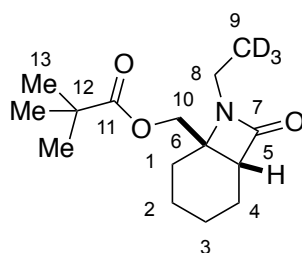
6.3 Experimental Procedures for the Synthesis of  $\beta$ -lactams from ATAs*cis-(7-ethyl-8-oxo-7-azabicyclo[4.2.0]octan-6-yl)methyl pivalate 567*

Prepared according to general procedure A using (1-(ethylamino)cyclohexyl)methyl pivalate **566** (72.4 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 5% ethyl acetate in petroleum ether to 30% ethyl acetate in petroleum ether) and filtration through a pad of activated charcoal (10% ethyl acetate in petroleum ether) gave the product as a colourless oil (58.2

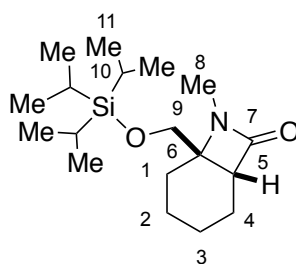


mg, 72%).  $R_f$  (30% ethyl acetate in petroleum ether): 0.29; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2937, 2872, 1727, 1481, 1459, 1399, 1376, 1282, 1228, 1148, 1035;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.25 (1 H, d,  $J = 11.8$  Hz,  $\text{H}_{10a}$ ), 4.01 (1 H, d,  $J = 12.0$  Hz,  $\text{H}_{10b}$ ), 3.19 (1 H, sxt,  $J = 7.1$  Hz,  $\text{H}_{8a}$ ), 3.10 (1 H, sxt,  $J = 7.1$  Hz,  $\text{H}_{8b}$ ), 2.97 (1 H, dd,  $J = 3.1, 5.6$  Hz,  $\text{H}_5$ ), 1.90 – 1.85 (1 H, m,  $\text{H}_{4a}$ ), 1.81 – 1.77 (1 H, m,  $\text{H}_{1a}$ ), 1.66 – 1.49 (6 H, m,  $\text{H}_{1b}$ ,  $\text{H}_2$ ,  $\text{H}_3$  and  $\text{H}_{4b}$ ), 1.20 – 1.17 (12 H, m,  $\text{H}_9$  and  $\text{H}_{13}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 178.2 ( $\text{C}_{11}$ ), 169.8 ( $\text{C}_7$ ), 66.6 ( $\text{C}_{10}$ ), 59.1 ( $\text{C}_6$ ), 49.7 ( $\text{C}_5$ ), 39.1 ( $\text{C}_{12}$ ), 34.5 ( $\text{C}_8$ ), 27.3 ( $\text{C}_{13}$ ), 25.3 ( $\text{C}_1$ ), 19.4 ( $\text{C}_4$ ), 18.7 ( $\text{C}_3$ ), 17.2 ( $\text{C}_2$ ), 14.3 ( $\text{C}_9$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  268.1908,  $\text{C}_{15}\text{H}_{26}\text{NO}_3$  requires 268.1907.

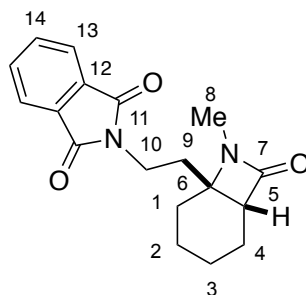
(*cis*-7-(ethyl-2,2,2- $d_3$ )-8-oxo-7-azabicyclo[4.2.0]octan-6-yl)methyl pivalate  $d_3$ -**567**



Prepared according to general procedure A using (1-((ethyl-2,2,2- $d_3$ )amino)cyclohexyl)methyl pivalate  $d_3$ -**566** (73.2 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 30% ethyl acetate in petroleum ether) gave the product as a pale yellow oil (54.9 mg, 68%).  $R_f$  (30% ethyl acetate in petroleum ether): 0.18; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2937, 2873, 1728, 1480, 1452, 1398, 1365, 1147, 1034;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.25 (1 H, d,  $J = 11.9$  Hz,  $\text{H}_{10a}$ ), 4.01 (1 H, d,  $J = 11.9$  Hz,  $\text{H}_{10b}$ ), 3.18 (1 H, d,  $J = 14.1$  Hz,  $\text{H}_{8a}$ ), 3.07 (1 H, d,  $J = 14.1$  Hz,  $\text{H}_{8b}$ ), 2.97 (1 H, dd,  $J = 3.2, 5.9$  Hz,  $\text{H}_5$ ), 1.91 – 1.84 (1 H, m,  $\text{H}_{4a}$ ), 1.81 – 1.77 (1 H, m,  $\text{H}_{1a}$ ), 1.68 – 1.47 (6 H, m,  $\text{H}_{1b}$ ,  $\text{H}_2$ ,  $\text{H}_3$  and  $\text{H}_{4b}$ ), 1.20 (9 H, s,  $\text{H}_{13}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 178.2 ( $\text{C}_{11}$ ), 169.9 ( $\text{C}_7$ ), 66.6 ( $\text{C}_{10}$ ), 59.1 ( $\text{C}_6$ ), 49.7 ( $\text{C}_5$ ), 39.1 ( $\text{C}_{12}$ ), 34.3 ( $\text{C}_8$ ), 27.3 ( $\text{C}_{13}$ ), 25.3 ( $\text{C}_1$ ), 19.4 ( $\text{C}_4$ ), 18.7 ( $\text{C}_3$ ), 17.2 ( $\text{C}_2$ ), 13.5 (spt,  $J = 19.5$  Hz,  $\text{C}_9$ ).  $^2\text{H}$  NMR (77 MHz,  $\text{CHCl}_3$  with 5%  $\text{CDCl}_3$ )  $\delta$ : 1.16 (s);  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  271.2098,  $\text{C}_{15}\text{H}_{23}\text{D}_3\text{NO}_3$  requires 271.2096

*cis*-7-methyl-6-(((triisopropylsilyl)oxy)methyl)-7-azabicyclo[4.2.0]octan-8-one **585c**

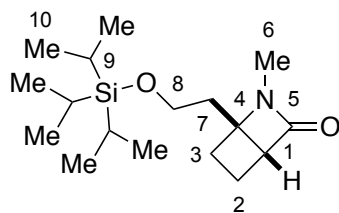
To a 250 mL round-bottomed flask equipped with large oval shaped stirrer bar was added Pd(OAc)<sub>2</sub> (168 mg, 0.75 mmol, 0.1 equiv), AgOAc (3.75 g, 22.5 mmol, 3 equiv), Xantphos (425 mg, 0.75 mmol, 0.1 equiv) and 1,4-benzoquinone (1.65 g, 15 mmol, 2 equiv). *N*-methyl-1-(((triisopropylsilyl)oxy)methyl)cyclohexan-1-amine **584c** (2.24 g, 7.5 mmol) was subsequently dissolved in toluene (30 mL) and added to the flask. The flask was sealed with a new septa and Teflon tape and purged with a balloon of CO (3 cycles). The flask was placed into a preheated oil bath at 80 °C and stirred vigorously for 18 hours. The flask was allowed to cool to room temperature, filtered over a plug of celite and washed with ethyl acetate. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (gradient elution: 5% ethyl acetate in petroleum ether to 30% ethyl acetate in petroleum ether) and subsequently by flash column chromatography over alumina (gradient elution: 5% ethyl acetate in petroleum ether to 30% ethyl acetate in petroleum ether) to afford the product as a colourless oil (1.98 g, 81%). *R<sub>f</sub>* (30% ethyl acetate in petroleum ether): 0.53; IR  $\nu_{\text{max}}$ /cm<sup>-1</sup> (film): 2941, 2865, 1746, 1463, 1418, 1387, 1334, 1295, 1247, 1116, 1092, 1066; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 3.74 (1 H, d, *J* = 10.1 Hz, H<sub>9a</sub>), 3.86 (1 H, d, *J* = 10.1 Hz, H<sub>9b</sub>), 2.92 – 2.90 (1 H, m, H<sub>5</sub>), 2.71 (3 H, s, H<sub>8</sub>), 1.88 – 1.77 (2 H, m, H<sub>1a</sub> and H<sub>4a</sub>), 1.62 – 1.45 (6 H, m, H<sub>1b</sub>, H<sub>2</sub>, H<sub>3</sub> and H<sub>4</sub>), 1.09 – 1.02 (21 H, m, H<sub>10</sub> and H<sub>11</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 170.6 (C<sub>7</sub>), 67.8 (C<sub>9</sub>), 60.2 (C<sub>6</sub>), 49.2 (C<sub>5</sub>), 25.1 (C<sub>8</sub>), 24.3 (C<sub>1</sub>), 19.7 (C<sub>4</sub>), 19.2 (C<sub>3</sub>), 18.1 (C<sub>11</sub>), 17.7 (C<sub>2</sub>), 12.0 (C<sub>10</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 326.2503, C<sub>18</sub>H<sub>36</sub>NO<sub>2</sub>Si requires 326.2510.

*N*-(2-(*cis*-7-methyl-8-oxo-7-azabicyclo[4.2.0]octan-6-yl)ethyl)phthalimide **585h**

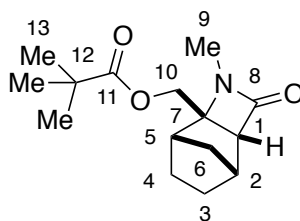
Prepared according to general procedure A using *N*-(2-(1-

(methylamino)cyclohexyl)ethyl)phthalimide **584h** (57.3 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 30% ethyl acetate in petroleum ether to 60% ethyl acetate in petroleum ether) and subsequently by flash column chromatography over alumina (gradient elution: 20% ethyl acetate in petroleum ether to 50% ethyl acetate in petroleum ether) gave the product as a white crystalline solid (74.5 mg, 80%) (Product contains 5 % impurity by  $^1\text{H}$  NMR spectroscopy).  $R_f$  (50% ethyl acetate in petroleum ether): 0.23; m.p. 124 – 126 °C; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2937, 2872, 1771, 1736, 1707, 1614, 1466, 1436, 1407, 1394, 1378, 1275, 1252, 1189, 1138, 1092;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.85 (2 H, dd,  $J = 3.1, 5.5$  Hz,  $\text{H}_{13}$ ), 7.72 (2 H, dd,  $J = 3.1, 5.5$  Hz,  $\text{H}_{14}$ ), 3.81 – 3.66 (2 H, m,  $\text{H}_{10}$ ), 3.08 – 3.06 (1 H, m,  $\text{H}_5$ ), 2.74 (3 H, s,  $\text{H}_8$ ), 2.09 – 2.01 (1 H, m,  $\text{H}_{9a}$ ), 1.97 – 1.89 (2 H, m,  $\text{H}_{9b}$  and  $\text{C}_{4a}$ ), 1.76 – 1.45 (7 H, m,  $\text{H}_1$ ,  $\text{H}_2$ ,  $\text{H}_3$  and  $\text{H}_{4b}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 170.0 ( $\text{C}_7$ ), 168.2 ( $\text{C}_{11}$ ), 134.3 ( $\text{C}_{14}$ ), 132.2 ( $\text{C}_{12}$ ), 123.5 ( $\text{C}_{13}$ ), 58.5 ( $\text{C}_6$ ), 51.4 ( $\text{C}_5$ ), 35.5 ( $\text{C}_9$ ), 33.5 ( $\text{C}_{10}$ ), 27.2 ( $\text{C}_1$ ), 24.5 ( $\text{C}_8$ ), 19.4 ( $\text{C}_4$ ), 18.2 ( $\text{C}_3$ ), 17.1 ( $\text{C}_2$ ); m/z HRMS found  $[\text{M} + \text{H}]^+$  313.1552,  $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_3$  requires 313.1552.

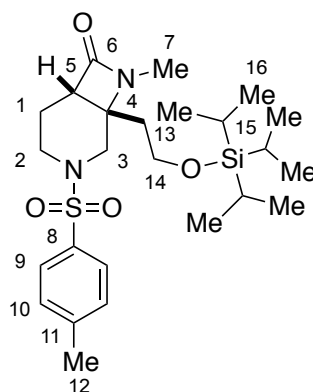
*cis*-2-methyl-1-(2-((triisopropylsilyl)oxy)ethyl)-2-azabicyclo[2.2.0]hexan-3-one **585k**



Prepared according to general procedure A using *N*-methyl-1-(2-((triisopropylsilyl)oxy)ethyl)cyclobutan-1-amine **584k** (85.7 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 5% ethyl acetate in petroleum ether to 30% ethyl acetate in petroleum ether) and subsequently by flash column chromatography over alumina (gradient elution: 5% ethyl acetate in petroleum ether to 30% ethyl acetate in petroleum ether) gave the product as a colourless oil (78.9 mg, 84%).  $R_f$  (30% ethyl acetate in petroleum ether): 0.37; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2942, 2866, 1744, 1463, 1413, 1378, 1292, 1246, 1225, 1187, 1097;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.75 (2 H, dt,  $J = 1.0, 6.3$  Hz,  $\text{H}_8$ ), 3.40 (1 H, dd,  $J = 2.2, 8.9$  Hz,  $\text{H}_1$ ), 2.75 (3 H, s,  $\text{H}_6$ ), 2.37 – 2.28 (1 H, m,  $\text{H}_{2a}$ ), 2.20 (1 H, dt,  $J = 5.5, 12.3$  Hz,  $\text{H}_{3a}$ ), 2.06 – 1.92 (2 H, m,  $\text{H}_{2b}$  and  $\text{H}_{3b}$ ), 1.90 (2 H, t,  $J = 6.3$  Hz,  $\text{H}_7$ ), 1.09 – 1.02 (21 H, m,  $\text{H}_9$  and  $\text{H}_{10}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 171.4 ( $\text{C}_5$ ), 62.5 ( $\text{C}_4$ ), 59.8 ( $\text{C}_8$ ), 52.8 ( $\text{C}_1$ ), 35.3 ( $\text{C}_7$ ), 27.1 ( $\text{C}_3$ ), 24.9 ( $\text{C}_6$ ), 18.1 ( $\text{C}_2$  and  $\text{C}_{10}$ ), 12.0 ( $\text{C}_9$ ); m/z HRMS found  $[\text{M} + \text{H}]^+$  312.2354,  $\text{C}_{17}\text{H}_{34}\text{NSi}$  requires 312.2353

*cis*-3-methyl-4-oxo-3-azatricyclo[4.2.1.0<sup>2,5</sup>]nonan-2-yl)methyl pivalate **585I**

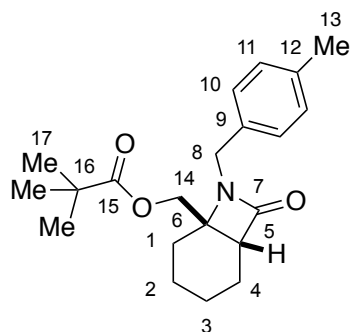
Prepared according to general procedure A using endo-2-(methylamino)norbornane-2-methyl pivalate **585I** (71.8 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 5% ethyl acetate in petroleum ether to 20% ethyl acetate in petroleum ether) and subsequently by flash column chromatography over alumina (gradient elution: 5% ethyl acetate in petroleum ether to 30% ethyl acetate in petroleum ether) gave the product as a colourless oil (55.0 mg, 69%).  $R_f$  (20% ethyl acetate in petroleum ether): 0.17; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2959, 2878, 1724, 1480, 1459, 1419, 1382, 1331, 1303, 1281, 1149;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.49 (1 H, d,  $J = 12.3$  Hz,  $\text{H}_{10a}$ ), 4.01 (1 H, d,  $J = 12.3$  Hz,  $\text{H}_{10b}$ ), 3.19 (1 H, d,  $J = 5.7$  Hz,  $\text{H}_1$ ), 2.73 (3 H, s,  $\text{H}_9$ ), 2.45 (1 H, br s,  $\text{H}_2$ ), 2.24 (1 H, app. d,  $J = 3.3$  Hz,  $\text{H}_5$ ), 1.77 (1 H, d,  $J = 10.6$  Hz,  $\text{H}_{6a}$ ), 1.67 – 1.53 (4 H, m,  $\text{H}_3$ ,  $\text{H}_{4a}$  and  $\text{H}_{6b}$ ), 1.44 – 1.39 (1 H, m,  $\text{H}_{4b}$ ), 1.19 (9 H, s,  $\text{H}_{13}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 178.2 ( $\text{C}_{11}$ ), 169.0 ( $\text{C}_8$ ), 69.1 ( $\text{C}_7$ ), 62.8 ( $\text{C}_{10}$ ), 61.3 ( $\text{C}_1$ ), 43.4 ( $\text{C}_6$ ), 39.3 ( $\text{C}_5$ ), 39.1 ( $\text{C}_{12}$ ), 36.5 ( $\text{C}_2$ ), 27.3 ( $\text{C}_{13}$ ), 27.1 ( $\text{C}_9$ ), 25.8 ( $\text{C}_3$ ), 24.3 ( $\text{C}_4$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  266.1752,  $\text{C}_{15}\text{H}_{24}\text{O}_3\text{N}$  requires 266.1751.

*cis*-8-methyl-3-tosyl-1-(2-((triisopropylsilyl)oxy)ethyl)-3,8-diazabicyclo[4.2.0]octan-7-one **587a**

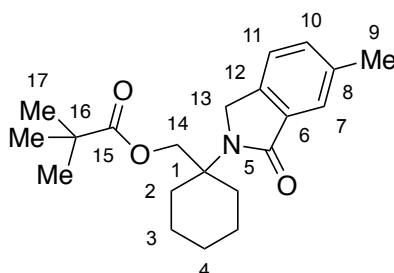
Prepared according to general procedure A using *N*-methyl-1-tosyl-3-(2-((triisopropylsilyl)oxy)ethyl)piperidin-3-amine **586a** (140.6 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 5% ethyl acetate in petroleum ether to 30% ethyl acetate in petroleum ether) and subsequently by flash column chromatography over alumina (gradient elution: 5% ethyl acetate in petroleum ether to 30% ethyl acetate in petroleum ether) gave the product as a colourless oil (87.0 mg, 59%).  $R_f$  (30% ethyl acetate in petroleum ether): 0.13; IR

$\nu_{\max}/\text{cm}^{-1}$  (film): 2943, 2866, 1744, 1598, 1463, 1421, 1390, 1338, 1250, 1162, 1092;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.65 (2 H, d,  $J = 8.3$  Hz,  $\text{H}_9$ ), 7.30 (2 H,  $J = 8.1$  Hz,  $\text{H}_{10}$ ), 3.81 – 3.76 (3 H, m,  $\text{H}_{3a}$  and  $\text{H}_{14}$ ), 3.49 (1 H, dt,  $J = 6.1, 11.6$  Hz,  $\text{H}_{2a}$ ), 3.19 (1 H, t,  $J = 3.7$  Hz,  $\text{H}_5$ ), 3.13 (1 H, ddd,  $J = 2.3, 7.1, 10.8$  Hz,  $\text{H}_{2b}$ ), 3.00 (1 H, d,  $J = 13.6$  Hz,  $\text{H}_{3b}$ ), 2.67 (3 H, s,  $\text{H}_7$ ), 2.41 (3 H, s,  $\text{H}_{12}$ ), 2.06 (1 H, dqt, 3.1, 14.9 Hz,  $\text{H}_{1a}$ ), 1.92 – 1.69 (3 H, m,  $\text{H}_{1b}$  and  $\text{H}_{13}$ ), 1.03 – 0.99 (21 H, m,  $\text{H}_{15}$  and  $\text{H}_{16}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 168.2 ( $\text{C}_6$ ), 143.6 ( $\text{C}_8$ ), 134.9 ( $\text{C}_{11}$ ), 129.9 ( $\text{C}_{10}$ ), 127.3 ( $\text{C}_9$ ), 59.4 ( $\text{C}_4$ ), 59.3 ( $\text{C}_{14}$ ), 50.6 ( $\text{C}_5$ ), 44.6 ( $\text{C}_3$ ), 40.9 ( $\text{C}_2$ ), 36.8 ( $\text{C}_{13}$ ), 24.4 ( $\text{C}_7$ ), 21.6 ( $\text{C}_{12}$ ), 19.5 ( $\text{C}_1$ ), 18.1 ( $\text{C}_{16}$ ), 11.9 ( $\text{C}_{15}$ );  $m/z$  HRMS found  $[\text{M} + \text{NH}_4]^+$  512.2964,  $\text{C}_{25}\text{H}_{46}\text{O}_4\text{N}_3\text{SSi}$  requires 512.2973.

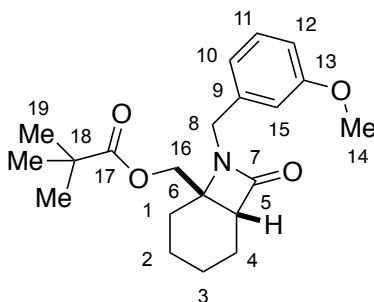
*cis*-7-(4-methylbenzyl)-8-oxo-7-azabicyclo[4.2.0]octan-6-yl)methyl pivalate **597a**



Prepared according to general procedure A using (1-((4-methylbenzyl)amino)cyclohexyl)methyl pivalate **595a** (95.2 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 25% ethyl acetate in petroleum ether) and subsequently by flash column chromatography over alumina (gradient elution: 100 % petroleum ether to 20% ethyl acetate in petroleum ether) gave the product as a colourless oil (32.7 mg, 32%).  $R_f$  (20% ethyl acetate in petroleum ether): 0.27; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2936, 2871, 1728, 1516, 1480, 1458, 1397, 1365, 1346, 1281, 1145, 1035;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.20 (2 H, d,  $J = 8.0$  Hz,  $\text{H}_{10}$ ), 7.10 (2 H, d,  $J = 8.0$  Hz,  $\text{H}_{11}$ ), 4.29 (1 H, d,  $J = 15.1$  Hz,  $\text{H}_{8a}$ ), 4.20 (1 H, d,  $J = 15.1$  Hz,  $\text{H}_{8b}$ ), 4.08 (1 H, d,  $J = 11.7$  Hz,  $\text{H}_{14a}$ ), 3.92 (1 H, d,  $J = 11.71$  Hz,  $\text{H}_{14b}$ ), 3.06 – 3.04 (1 H, m,  $\text{H}_5$ ), 2.31 (3 H, s,  $\text{H}_{13}$ ), 1.93 – 1.88 (1 H, m,  $\text{H}_{4a}$ ), 1.67 – 1.56 (3 H, m,  $\text{H}_{1a}$ ,  $\text{H}_{3a}$  and  $\text{H}_{4b}$ ), 1.49 – 1.38 (3 H, m,  $\text{H}_{1b}$ ,  $\text{H}_{2a}$  and  $\text{H}_{3b}$ ), 1.29 – 1.23 (1 H, m,  $\text{H}_{2b}$ ), 1.17 (9 H, s,  $\text{H}_{17}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 178.1 ( $\text{C}_{15}$ ), 170.0 ( $\text{C}_7$ ), 137.5 ( $\text{C}_{12}$ ), 133.7 ( $\text{C}_9$ ), 129.5 ( $\text{C}_{11}$ ), 128.5 ( $\text{C}_{10}$ ), 66.1 ( $\text{C}_{14}$ ), 59.8 ( $\text{C}_6$ ), 50.0 ( $\text{C}_5$ ), 43.6 ( $\text{C}_8$ ), 39.0 ( $\text{C}_{16}$ ), 27.3 ( $\text{C}_{17}$ ), 25.1 ( $\text{C}_1$ ), 21.2 ( $\text{C}_{13}$ ), 19.6 ( $\text{C}_4$ ), 18.7 ( $\text{C}_3$ ), 17.1 ( $\text{C}_2$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  344.2222,  $\text{C}_{21}\text{H}_{30}\text{NO}_3$  requires 344.2220.

*(1-(6-methyl-1-oxoisindolin-2-yl)cyclohexyl)methyl pivalate* **596a**

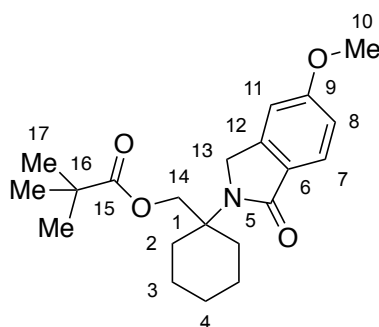
Prepared according to general procedure A using (1-((4-methylbenzyl)amino)cyclohexyl)methyl pivalate **595a** (95.2 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 25% ethyl acetate in petroleum ether) and subsequently by flash column chromatography over alumina (gradient elution: 100 % petroleum ether to 20% ethyl acetate in petroleum ether) gave the product as a colourless oil (51.7 mg, 51%).  $R_f$  (20% ethyl acetate in petroleum ether): 0.45; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2933, 2866, 1727, 1680, 1628, 1497, 1480, 1449, 1385, 1321, 1281, 1229, 1194, 1149, 1035;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.58 (1 H, s,  $\text{H}_7$ ), 7.34 – 7.26 (2 H, m,  $\text{H}_{10}$  and  $\text{H}_{11}$ ), 4.52 (2 H, s,  $\text{H}_{13}$ ), 4.38 (2 H, s,  $\text{H}_{14}$ ), 2.55 – 2.52 (2 H, m,  $\text{H}_{2a}$ ), 2.43 (3 H, s,  $\text{H}_9$ ), 1.78 – 1.73 (2 H, m,  $\text{H}_{2b}$ ), 1.68 – 1.42 (6 H, m,  $\text{H}_3$  and  $\text{H}_4$ ), 1.10 (9 H, s,  $\text{H}_{17}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 178.3 ( $\text{C}_{15}$ ), 169.8 ( $\text{C}_5$ ), 138.3 ( $\text{C}_{12}$ ), 138.0 ( $\text{C}_8$ ), 134.2 ( $\text{C}_6$ ), 132.4 ( $\text{C}_{10}$ ), 123.7 ( $\text{C}_7$ ), 122.0 ( $\text{C}_{11}$ ), 67.7 ( $\text{C}_{14}$ ), 59.4 ( $\text{C}_1$ ), 49.0 ( $\text{C}_{13}$ ), 39.0 ( $\text{C}_{16}$ ), 31.9 ( $\text{C}_2$ ), 27.3 ( $\text{C}_{17}$ ), 25.8 ( $\text{C}_4$ ), 22.3 ( $\text{C}_3$ ), 21.5 ( $\text{C}_9$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  344.2221,  $\text{C}_{21}\text{H}_{30}\text{NO}_3$  requires 344.2220.

*cis-7-(3-methoxybenzyl)-8-oxo-7-azabicyclo[4.2.0]octan-6-yl)methyl pivalate* **597b**

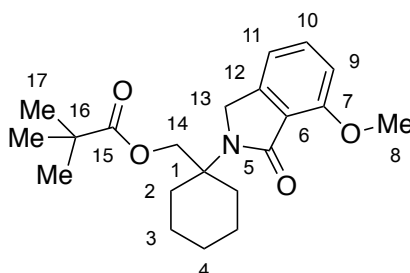
Prepared according to general procedure A using (1-((3-methoxybenzyl)amino)cyclohexyl)methyl pivalate **595b** (99.9 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 30% ethyl acetate in petroleum ether) and subsequently by preparative thin-layer chromatography (40% ethyl acetate in petroleum ether) gave the product as a colourless oil (16.5 mg, 15%).  $R_f$  (30% ethyl acetate in petroleum ether): 0.18; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2937, 2871, 1728, 1601, 1587, 1490, 1480, 1456, 1397, 1366, 1344, 1282, 1263, 1146, 1038;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.22 (1 H, t,  $J = 8.1$  Hz,  $\text{H}_{11}$ ), 6.90 – 6.87 (2 H, m,  $\text{H}_{10}$  and  $\text{H}_{15}$ ), 6.80 (1 H, dd,  $J =$

2.4, 8.1 Hz, H<sub>12</sub>), 4.31 (1 H, d,  $J = 15.4$  Hz, H<sub>8a</sub>), 4.21 (1 H, d,  $J = 15.1$  Hz, H<sub>8b</sub>), 4.13 (1 H, d,  $J = 11.9$  Hz, H<sub>16a</sub>), 4.12 (1 H, d,  $J = 11.9$  Hz, H<sub>16b</sub>), 3.79 (3 H, s, H<sub>14</sub>), 3.07 (1 H, dd,  $J = 3.5, 6.1$  Hz, H<sub>5</sub>), 1.94 – 1.89 (1 H, m, H<sub>4a</sub>), 1.70 – 1.57 (3 H, m, H<sub>1a</sub>, H<sub>3a</sub> and H<sub>4b</sub>), 1.51 – 1.39 (3 H, m, H<sub>1b</sub>, H<sub>2a</sub> and H<sub>3b</sub>), 1.32 – 1.25 (1 H, m, H<sub>2b</sub>), 1.17 (9 H, s, H<sub>19</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 178.1 (C<sub>17</sub>), 170.1 (C<sub>5</sub>), 160.0 (C<sub>13</sub>), 138.4 (C<sub>9</sub>), 129.8 (C<sub>11</sub>), 120.8 (C<sub>10</sub>), 114.0 (C<sub>15</sub>), 113.4 (C<sub>12</sub>), 66.2 (C<sub>16</sub>), 59.9 (C<sub>6</sub>), 55.4 (C<sub>14</sub>), 50.1 (C<sub>5</sub>), 43.9 (C<sub>8</sub>), 39.1 (C<sub>18</sub>), 27.3 (C<sub>19</sub>), 25.1 (C<sub>1</sub>), 19.7 (C<sub>4</sub>), 18.7 (C<sub>3</sub>), 17.2 (C<sub>2</sub>); m/z HRMS found  $[M + H]^+$  360.2169, C<sub>21</sub>H<sub>30</sub>NO<sub>4</sub> requires 360.2172.

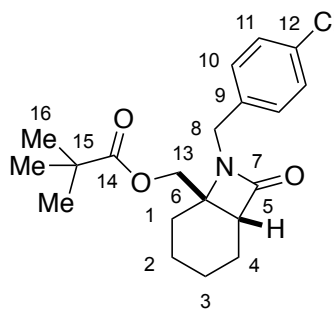
*(1-(5-methoxy-1-oxoisindolin-2-yl)cyclohexyl)methyl pivalate p-596b*



Prepared according to general procedure A using (1-((3-methoxybenzyl)amino)cyclohexyl)methyl pivalate **595b** (99.9 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 30% ethyl acetate in petroleum ether) and subsequently by flash column chromatography over alumina (gradient elution: 100 % petroleum ether to 20% ethyl acetate in petroleum ether) gave the product as a colourless oil that solidified on standing (56.0 mg, 51%).  $R_f$  (30% ethyl acetate in petroleum ether): 0.45; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2934, 2864, 1727, 1675, 1613, 1491, 1480, 1384, 1335, 1283, 1261, 1151, 1091, 1027; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.68 (1 H, d,  $J = 8.6$  Hz, H<sub>11</sub>), 6.95 (1 H, dd,  $J = 2.2, 8.4$  Hz, H<sub>8</sub>), 6.89 (1 H, d,  $J = 2.2$  Hz, H<sub>7</sub>), 4.51 (2 H, s, H<sub>13</sub>), 4.36 (2 H, s, H<sub>14</sub>), 3.85 (3 H, s, H<sub>10</sub>), 2.53 (2 H, app d,  $J = 13.3$  Hz, H<sub>2a</sub>), 1.76 – 1.40 (8 H, m, H<sub>2b</sub>, H<sub>3</sub> and H<sub>4</sub>), 1.09 (9 H, s, H<sub>17</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 178.2 (C<sub>15</sub>), 169.6 (C<sub>5</sub>), 162.7 (C<sub>9</sub>), 143.2 (C<sub>6</sub>), 126.7 (C<sub>12</sub>), 124.8 (C<sub>11</sub>), 114.7 (C<sub>8</sub>), 107.0 (C<sub>7</sub>), 67.7 (C<sub>14</sub>), 59.3 (C<sub>1</sub>), 55.7 (C<sub>10</sub>), 48.9 (C<sub>13</sub>), 38.9 (C<sub>16</sub>), 31.9 (C<sub>2</sub>), 27.3 (C<sub>17</sub>), 25.7 (C<sub>4</sub>), 22.3 (C<sub>3</sub>); m/z HRMS found  $[M + H]^+$  360.2170, C<sub>21</sub>H<sub>30</sub>NO<sub>4</sub> requires 360.2169

*(1-(7-methoxy-1-oxoisindolin-2-yl)cyclohexyl)methyl pivalate* **596b**

Prepared according to general procedure A using (1-((3-methoxybenzyl)amino)cyclohexyl)methyl pivalate **595b** (99.9 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 30% ethyl acetate in petroleum ether) and subsequently by preparative thin-layer chromatography (40% ethyl acetate in petroleum ether) gave the product as a colourless oil (9.0 mg, 8%).  $R_f$  (30% ethyl acetate in petroleum ether): 0.15; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2936, 2861, 1725, 1674, 1610, 1488, 1459, 1389, 1325, 1284, 1268, 1153, 1083;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.45 (1 H, t,  $J = 7.9$  Hz,  $\text{H}_{10}$ ), 6.97 (1 H, d,  $J = 7.4$  Hz,  $\text{H}_{11}$ ), 6.86 (1 H, d,  $J = 7.4$  Hz,  $\text{H}_9$ ), 4.55 (2 H, s,  $\text{H}_{13}$ ), 4.43 (2 H, s,  $\text{H}_{14}$ ), 3.95 (3 H, s,  $\text{H}_8$ ), 2.52 (2 H, app d,  $J = 13.5$  Hz,  $\text{H}_{2a}$ ), 1.74 – 1.39 (8 H, m,  $\text{H}_{2b}$ ,  $\text{H}_3$  and  $\text{H}_4$ ), 1.10 (9 H, s,  $\text{H}_{17}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 178.2 ( $\text{C}_{15}$ ), 168.8 ( $\text{C}_5$ ), 157.5 ( $\text{C}_7$ ), 144.1 ( $\text{C}_6$ ), 133.0 ( $\text{C}_{10}$ ), 121.0 ( $\text{C}_{12}$ ), 114.4 ( $\text{C}_{11}$ ), 109.8 ( $\text{C}_9$ ), 67.7 ( $\text{C}_{14}$ ), 59.2 ( $\text{C}_1$ ), 55.9 ( $\text{C}_8$ ), 49.0 ( $\text{C}_{13}$ ), 38.9 ( $\text{C}_{16}$ ), 31.7 ( $\text{C}_2$ ), 27.4 ( $\text{C}_{17}$ ), 25.8 ( $\text{C}_4$ ), 22.4 ( $\text{C}_3$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  360.2170,  $\text{C}_{21}\text{H}_{30}\text{NO}_4$  requires 360.2169.

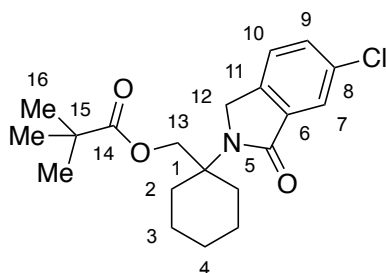
*cis-7-(4-chlorobenzyl)-8-oxo-7-azabicyclo[4.2.0]octan-6-yl)methyl pivalate* **597c**

Prepared according to general procedure A using (1-((4-chlorobenzyl)amino)cyclohexyl)methyl pivalate **595c** (101.2 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 25% ethyl acetate in petroleum ether) and subsequently by flash column chromatography over alumina (gradient elution: 100 % petroleum ether to 20% ethyl acetate in petroleum ether) gave the product as a colourless oil (56.3 mg, 52%).  $R_f$  (20% ethyl acetate in petroleum ether): 0.28; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2936, 2871, 1730, 1492, 1480, 1458, 1396, 1365, 1281, 1146, 1092, 1035;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.30 – 7.25 (4 H, m,  $\text{H}_{10}$  and  $\text{H}_{11}$ ), 4.29 (1 H,

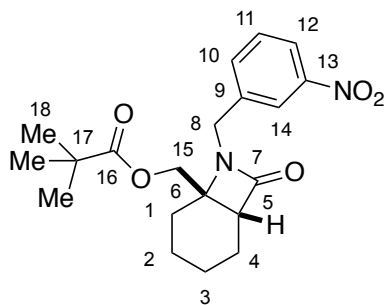


d,  $J = 15.3$  Hz,  $H_{8a}$ ), 4.18 (1 H, d,  $J = 15.3$  Hz,  $H_{8b}$ ), 4.15 (1 H, d,  $J = 11.8$  Hz,  $H_{13a}$ ), 3.93 (1 H, d,  $J = 11.8$  Hz,  $H_{13b}$ ), 3.07 (1 H, dd,  $J = 3.5, 6.3$  Hz,  $H_5$ ), 1.93 – 1.86 (1 H, m,  $H_{4a}$ ), 1.69 – 1.55 (3 H, m,  $H_{1a}$ ,  $H_{3a}$  and  $H_{4b}$ ), 1.51 – 1.39 (3 H, m,  $H_{1b}$ ,  $H_{2a}$  and  $H_{3b}$ ), 1.26 – 1.19 (1 H, m,  $H_{2b}$ ), 1.16 (9 H, s,  $H_{16}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 178.1 ( $C_{14}$ ), 170.1 ( $C_7$ ), 135.5 ( $C_9$ ), 133.7 ( $C_{12}$ ), 129.8 ( $C_{10}$ ), 129.0 ( $C_{11}$ ), 66.0 ( $C_{13}$ ), 59.9 ( $C_6$ ), 50.0 ( $C_5$ ), 43.2 ( $C_8$ ), 39.0 ( $C_{15}$ ), 27.2 ( $C_{16}$ ), 25.1 ( $C_1$ ), 19.6 ( $C_4$ ), 18.7 ( $C_3$ ), 17.1 ( $C_2$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  364.1677  $\{^{35}\text{Cl}\}$ ,  $\text{C}_{20}\text{H}_{27}\text{ClNO}_3$  requires 364.1674  $\{^{35}\text{Cl}\}$ .

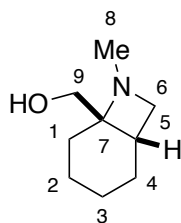
*(1-(6-chloro-1-oxoisindolin-2-yl)cyclohexyl)methyl pivalate* **596c**



Prepared according to general procedure A using (1-((4-chlorobenzyl)amino)cyclohexyl)methyl pivalate **595c** (101.2 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 25% ethyl acetate in petroleum ether) and subsequently by flash column chromatography over alumina (gradient elution: 100 % petroleum ether to 20% ethyl acetate in petroleum ether) gave the product as colourless needles (13.0 mg, 12%).  $R_f$  (20% ethyl acetate in petroleum ether): 0.47; m.p. 112 °C (sharp); IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2934, 2867, 1729, 1687, 1449, 1386, 1318, 1282, 1263, 1205, 1152, 1036;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.75 (1 H, d,  $J = 1.8$  Hz,  $H_7$ ), 7.49 (1 H, dd,  $J = 1.8, 8.0$  Hz,  $H_9$ ), 7.35 (1 H, d,  $J = 8.0$  Hz,  $H_{10}$ ), 4.54 (2 H, s,  $H_{12}$ ), 4.38 (2 H, s,  $H_{13}$ ), 2.51 (2 H, m,  $H_{2a}$ ), 1.77 (2 H, ddd,  $J = 3.0, 9.5, 12.6$  Hz,  $H_{2b}$ ), 1.66 – 1.60 (3 H, m,  $H_{3a}$  and  $H_{4a}$ ), 1.55 – 1.42 (3 H, m,  $H_{3b}$  and  $H_{4b}$ ), 1.10 (9 H, s,  $H_{16}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 178.2 ( $C_{14}$ ), 168.3 ( $C_5$ ), 139.1 ( $C_{11}$ ), 135.8 ( $C_8$ ), 134.4 ( $C_6$ ), 131.6 ( $C_9$ ), 123.7 ( $C_7$ ), 123.7 ( $C_{10}$ ), 67.6 ( $C_{13}$ ), 59.8 ( $C_1$ ), 48.8 ( $C_{12}$ ), 39.0 ( $C_{15}$ ), 31.9 ( $C_2$ ), 27.3 ( $C_{16}$ ), 25.7 ( $C_4$ ), 22.3 ( $C_3$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  364.1674  $\{^{35}\text{Cl}\}$ ,  $\text{C}_{20}\text{H}_{27}\text{ClNO}_3$  requires 364.1677  $\{^{35}\text{Cl}\}$ .

*cis*-7-(3-nitrobenzyl)-8-oxo-7-azabicyclo[4.2.0]octan-6-yl)methyl pivalate **597d**

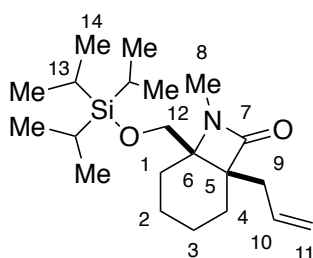
Prepared according to general procedure A using (1-((3-nitrobenzyl)amino)cyclohexyl)methyl pivalate **595d** (104.5 mg, 0.3 mmol). Purification by flash column chromatography (gradient elution: 100% petroleum ether to 35% ethyl acetate in petroleum ether) gave the product as a pale yellow oil (52.1 mg, 46%).  $R_f$  (20% ethyl acetate in petroleum ether): 0.12; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2937, 2871, 1728, 1529, 1480, 1461, 1397, 1348, 1281, 1145, 1097, 1035;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.18 – 8.13 (2 H, m,  $\text{H}_{12}$  and  $\text{H}_{14}$ ), 7.73 (1 H, d,  $J = 7.8$  Hz,  $\text{H}_{10}$ ), 7.52 (1 H, t,  $J = 7.3$  Hz,  $\text{H}_{11}$ ), 4.40 (1 H, d,  $J = 15.5$  Hz,  $\text{H}_{8a}$ ), 4.34 (1 H, d,  $J = 15.1$  Hz,  $\text{H}_{8b}$ ), 4.21 (1 H, d,  $J = 11.9$  Hz,  $\text{H}_{15a}$ ), 3.96 (1 H, d,  $J = 11.9$  Hz,  $\text{H}_{15b}$ ), 3.10 (1 H, dd,  $J = 3.7, 6.7$  Hz,  $\text{H}_5$ ), 1.95 – 1.88 (1 H, m,  $\text{H}_{4a}$ ), 1.72 – 1.43 (6 H, m,  $\text{H}_1$ ,  $\text{H}_{2a}$ ,  $\text{H}_3$  and  $\text{H}_{4b}$ ), 1.30 – 1.22 (1 H, m,  $\text{H}_{2b}$ ), 1.14 (9 H, s,  $\text{H}_{18}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 178.0 ( $\text{C}_{16}$ ), 170.4 ( $\text{C}_7$ ), 148.5 ( $\text{C}_{13}$ ), 139.2 ( $\text{C}_9$ ), 134.5 ( $\text{C}_{10}$ ), 130.0 ( $\text{C}_{11}$ ), 123.0 ( $\text{C}_{10}$  or  $\text{C}_{14}$ ), 122.9 ( $\text{C}_{10}$  or  $\text{C}_{14}$ ), 66.1 ( $\text{C}_{15}$ ), 60.2 ( $\text{C}_6$ ), 50.1 ( $\text{C}_5$ ), 43.2 ( $\text{C}_8$ ), 39.0 ( $\text{C}_{17}$ ), 27.2 ( $\text{C}_{18}$ ), 25.2 ( $\text{C}_1$ ), 19.6 ( $\text{C}_4$ ), 18.7 ( $\text{C}_3$ ), 17.2 ( $\text{C}_2$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  375.1916,  $\text{C}_{20}\text{H}_{27}\text{N}_2\text{O}_5$  requires 375.1914.

*cis*-7-methyl-7-azabicyclo[4.2.0]octan-6-yl)methanol **600**

To a solution of  $\text{AlCl}_3$  (120 mg, 0.9 mmol) in anhydrous diethyl ether (2 mL) was added lithium aluminium hydride (34 mg, 0.9 mmol) carefully at 0 °C under  $\text{N}_2$ . The reaction mixture was stirred at 0 °C for 10 min and subsequently refluxed for 30 min. *cis*-7-methyl-6-(((triisopropylsilyl)oxy)methyl)-7-azabicyclo[4.2.0]octan-8-one **585c** (97.6 mg, 0.3 mmol) in anhydrous diethyl ether (2 mL) was added dropwise and refluxed for 4 h. The reaction was cooled to room temperature and quenched with 10% aqueous NaOH (1 mL). The aqueous was extracted with diethyl ether (3 x 50 mL), dried over  $\text{Na}_2\text{SO}_4$  and the solvent removed *in vacuo* (volatile!) to obtain

the title compound as a colourless oil (41.9 mg, 90%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3366 (br), 2926, 2855, 1481, 1450, 1374, 1339, 1274, 1186, 1158, 1120, 1087, 1063;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.33 (1 H, d,  $J = 11.3$  Hz,  $\text{H}_{9a}$ ), 3.21 (1 H, dd  $J = 5.8, 7.3$  Hz,  $\text{H}_{6a}$ ), 3.09 (1 H, d,  $J = 11.3$  Hz,  $\text{H}_{9b}$ ), 2.79 (1 H, dd  $J = 5.8, 9.7$  Hz,  $\text{H}_{6b}$ ), 2.74 – 2.69 (1 H, m,  $\text{H}_5$ ), 2.11 (3 H, s,  $\text{H}_8$ ), 1.89 (1 H, td,  $J = 4.2, 13.6$  Hz,  $\text{H}_{1a}$ ), 1.70 – 1.65 (1 H, m,  $\text{H}_{2a}$ ), 1.59 – 1.54 (1 H, m,  $\text{C}_{4a}$ ), 1.51 – 1.47 (1 H, m,  $\text{C}_{3a}$ ), 1.43 – 1.32 (2 H, m,  $\text{C}_{3b}$  and  $\text{C}_{4b}$ ), 1.25 – 1.23 (1 H, m,  $\text{H}_{1b}$ ), 1.04 – 1.96 (1 H, m,  $\text{H}_{2b}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 67.8 ( $\text{C}_7$ ), 64.1 ( $\text{C}_9$ ), 54.2 ( $\text{C}_6$ ), 35.1 ( $\text{C}_8$ ), 29.9 ( $\text{C}_5$ ), 23.8 ( $\text{C}_1$  or  $\text{C}_3$ ), 23.7 ( $\text{C}_1$  or  $\text{C}_3$ ), 22.2 ( $\text{C}_4$ ), 21.4 ( $\text{C}_2$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  156.1382,  $\text{C}_9\text{H}_{18}\text{NO}$  requires 156.1383.

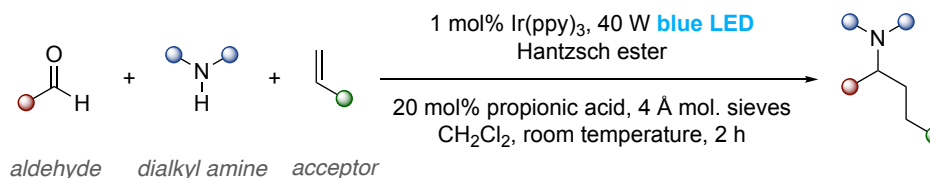
*cis*-1-allyl-6-(((triisopropylsilyl)oxy)methyl)-7-methyl-7-azabicyclo[4.2.0]octan-8-one **599**



To a solution of *cis*-7-methyl-6-(((triisopropylsilyl)oxy)methyl)-7-azabicyclo[4.2.0]octan-8-one **585c** (97.6 mg, 0.3 mmol) in anhydrous tetrahydrofuran (3 mL) was added a solution of freshly prepared LiHMDS (0.61 M, 0.75 mmol, 1.23 mL) dropwise at  $-78$  °C (dry ice/acetone bath) under  $\text{N}_2$ . The solution was stirred at  $-78$  °C for 2 hours and allyl bromide (104  $\mu\text{L}$ , 1.2 mmol) was added in one portion. The solution was warmed to room temperature over 16 hours and was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (3 mL). The organic layer was separated and the aqueous was extracted with diethyl ether (3 x 10 mL). The organics were combined, washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and the solvent removed *in vacuo*. The crude oil was purified by flash column chromatography (gradient elution: 5% ethyl acetate in petroleum ether to 25% ethyl acetate in petroleum ether) to afford the product as a colourless oil (86.8 mg, 79%).  $R_f$  (20% ethyl acetate in petroleum ether): 0.43; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2942, 2866, 1744, 1640, 1463, 1417, 1383, 1100, 1060;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.91 – 5.83 (1 H, m,  $\text{H}_{10}$ ), 5.06 – 5.02 (2 H, m,  $\text{H}_{11}$ ), 3.95 (1 H, d,  $J = 9.9$  Hz,  $\text{H}_{12a}$ ), 3.83 (1 H, d,  $J = 9.9$  Hz,  $\text{H}_{12b}$ ), 2.78 (3 H, s,  $\text{H}_8$ ), 2.49 (1 H, app. dd,  $J = 6.6, 14.5$  Hz,  $\text{H}_{9a}$ ), 2.32 (1 H, app. dd,  $J = 7.8, 14.5$  Hz,  $\text{H}_{9b}$ ), 2.03 (1 H, app. dd, 5.9, 12.4 Hz,  $\text{H}_{4a}$ ), 1.70 (1 H, dt,  $J = 3.4, 12.7$  Hz,  $\text{H}_{1a}$ ), 1.65 – 1.39 (6 H, m,  $\text{H}_{1b}$ ,  $\text{H}_2$ ,  $\text{H}_3$  and  $\text{H}_{4b}$ ), 1.09 – 1.05 (21 H, m,  $\text{H}_{13}$  and  $\text{H}_{14}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 172.6 ( $\text{C}_7$ ), 134.5 ( $\text{C}_{10}$ ), 117.7 ( $\text{C}_{11}$ ), 67.3 ( $\text{C}_{12}$ ), 64.3 ( $\text{C}_6$ ), 57.7 ( $\text{C}_5$ ), 35.5 ( $\text{C}_9$ ), 26.0 ( $\text{C}_8$ ), 25.6 ( $\text{C}_1$ ), 23.4 ( $\text{C}_4$ ), 18.1 ( $\text{C}_{14}$ ), 17.8 ( $\text{C}_3$ ), 16.3 ( $\text{C}_2$ ), 12.0 ( $\text{C}_{13}$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  366.2824,  $\text{C}_{21}\text{H}_{40}\text{NO}_2\text{Si}$  requires 366.2823.

## 6.4 Experimental Procedures for the Photocatalytic Synthesis of Tertiary Alkylamines

## General Procedure B for the photocatalytic synthesis of tertiary alkylamines



A 4 mL PTFE/Silicone-lined septa screw cap (PP) clear glass vial equipped with magnetic stirrer bar (10 mm, cylindrical) was charged with all solid reagents, *fac*-Ir(ppy)<sub>3</sub> (1.4 mg, 2 μmol), 4Å MS (100 mg) and ethyl-HEH **126** (76 mg, 0.3 mmol) or MeOEt-HEH **665** (94 mg, 0.3 mmol), under air. The vial was sealed and a needle was inserted through the septa and the contents evacuated/backfilled with N<sub>2</sub> (3 cycles). Anhydrous dichloromethane (2 mL) was added followed by the remaining liquid reagents, amine (0.2 mmol), aldehyde (0.22 – 0.4 mmol), alkene acceptor (0.22 – 0.4 mmol) and propanoic acid (3 μL, 40 μmol). The vial was sealed with additional parafilm™ and secured upon an upturned crystallizing basin using double-sided tape, in the center of a stirrer/hotplate. The Kessil lamp was positioned 5 cm from the vial along with a desk-fan for cooling. The vial was irradiated for a period of 2 hours with vigorous stirring (600-800 rpm), over which time the color of the reaction mixture (under light) typically turned from dark red/brown to bright yellow, indicating the consumption of the Hantzsch ester and completion of the reaction. Upon completion, the reaction mixture was analyzed by TLC and either directly loaded onto the column (in the case of dichloromethane/Et<sub>3</sub>N as an eluent) or filtered and the solvent removed *in vacuo* for purification using ethyl acetate/petroleum ether as an eluent.

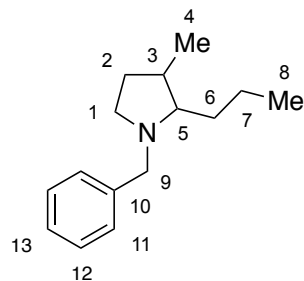
*From enamines:* The amine and aldehyde components can be replaced by the preformed enamine.

*From amine hydrochloride salts:* If amine hydrochloride salts are used, one equivalent of triethylamine was added to the reaction prior to irradiation.

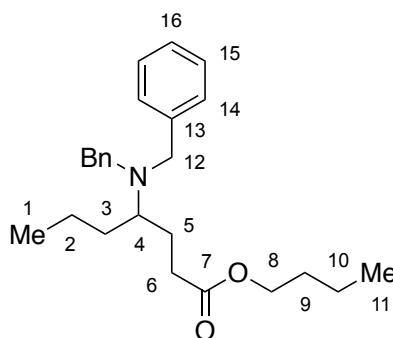
*General Procedure C for the photocatalytic synthesis of tertiary alkylamines using paraformaldehyde:*

The reaction is set up as in general procedure 2; however, prior to irradiation the reaction mixture is heated in an oil bath at 45 °C for one hour in the dark (foil covered).

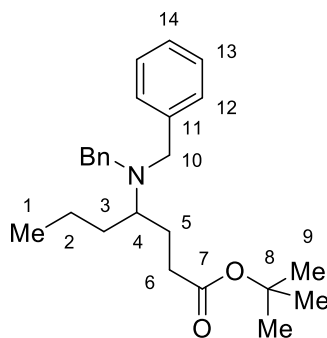
*1-benzyl-3-methyl-2-propylpyrrolidine* **650**



Prepared according to modified general procedure B using *N*-benzylbut-3-en-1-amine **648** (32 mg, 0.2 mmol) and butyraldehyde (20  $\mu$ L, 0.22 mmol) with a 30 W CFL bulb for 16 hours. The crude reaction mixture was filtered, the solvent removed *in vacuo* and subsequently dissolved in a solution of lithium hydroxide monohydrate (84 mg, 20 mmol) in tetrahydrofuran/water (6 mL, 5:1). The mixture was heated to a vigorous reflux for 2 hours, cooled to room temperature and diluted with saturated aqueous NaHCO<sub>3</sub> (10 mL). The aqueous was extracted with ethyl acetate (3 x 10 mL) and the organic combined and washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent removed *in vacuo* to afford the product as a colourless oil (27 mg, 62%, *cis/trans* 2.4:1 d.r. by GC-MS). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2956, 2931, 2871, 1718, 1678, 1643, 1494, 1453, 1375, 1262, 1072, 1027; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.34 – 7.20 (5 H, m, H<sub>11</sub>, H<sub>12</sub> and H<sub>13</sub>), [4.03 (d, *J* = 13.2 Hz, *cis*), 4.01 (d, *J* = 12.9 Hz, *trans*), total 1 H, H<sub>9a</sub>], [3.21 (d, *J* = 13.2 Hz, *cis*), 3.13 (d, *J* = 12.9 Hz, *trans*), total 1 H, H<sub>9b</sub>], [2.92 (dt, *J* = 3.2, 8.8 Hz, *cis*), 2.84 – 2.80 (m, *trans*), total 1 H, H<sub>1a</sub>], [2.40 – 2.36 (H<sub>5</sub>, *cis*), 2.23 – 2.08 (H<sub>3</sub>, *cis*), (H<sub>1b</sub>), 1.97 – 1.91 (H<sub>5</sub>, *trans*), (H<sub>3</sub>, *trans*), (H<sub>2a</sub> or H<sub>6a</sub>), 1.90 – 1.83 (H<sub>2a</sub> or H<sub>6a</sub>), total 4 H], 1.61 – 1.29 (4 H, m, H<sub>2b</sub>, H<sub>6b</sub> and H<sub>7</sub>), 1.00 – 0.93 (6 H, m, H<sub>4</sub> and H<sub>8</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 140.4 (C<sub>10</sub>, *cis*), 140.1 (C<sub>10</sub>, *trans*), 129.1 (C<sub>11</sub>, *trans*), 128.9 (C<sub>11</sub>, *cis*), 128.3 (C<sub>12</sub>, *trans*), 128.2 (C<sub>12</sub>, *cis*), 126.8 (C<sub>13</sub>, *trans*), 126.7 (C<sub>13</sub>, *cis*), 72.2 (C<sub>5</sub>, *trans*), 66.8 (C<sub>5</sub>, *cis*), 59.2 (C<sub>9</sub>, *trans*), 59.1 (C<sub>9</sub>, *cis*), 53.0 (C<sub>1</sub>, *cis*), 52.6 (C<sub>1</sub>, *trans*), 37.5 (C<sub>3</sub>, *trans*), 35.2, 34.6 (C<sub>3</sub>, *cis*), 32.0, 31.7, 31.5, 20.8, 20.2, 18.8, 16.1, 14.9, 14.8; *m/z* HRMS found [M + H]<sup>+</sup> 218.1910, C<sub>15</sub>H<sub>24</sub>N requires 218.1903. Data consistent with literature<sup>569</sup>.

*butyl 4-(dibenzylamino)heptanoate 656*

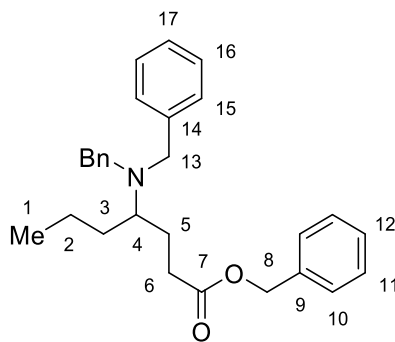
Prepared according to general procedure B using dibenzylamine (39  $\mu\text{L}$ , 0.2 mmol), butyraldehyde (20  $\mu\text{L}$ , 0.22 mmol) and *n*-butyl acrylate (32  $\mu\text{L}$ , 0.22 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (65 mg, 85%).  $R_f$  (5% EtOAc in P.E.): 0.21; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3027, 2957, 2932, 2870, 1732, 1602, 1494, 1453, 1360, 1244, 1170, 1141, 1072, 951, 744, 697.  $^1\text{H}$  NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.40 – 7.18 (10 H, m, H<sub>14,15,16</sub>), 4.07 – 3.96 (2 H, m, H<sub>8</sub>), 3.69 (2 H, d,  $J = 13.7$  Hz, H<sub>12a</sub>), 3.49 (2 H, d,  $J = 13.7$  Hz, H<sub>12b</sub>), 2.56 – 2.43 (2 H, m, H<sub>6a,4</sub>), 2.33 – 2.23 (1 H, m, H<sub>6b</sub>), 1.89 – 1.78 (1 H, m, H<sub>5a</sub>), 1.75 – 1.64 (2 H, m, H<sub>5b,3a</sub>), 1.63 – 1.54 (2 H, m, H<sub>9</sub>), 1.44 – 1.32 (4 H, m, H<sub>2,10</sub>), 1.28 – 1.16 (1 H, m, H<sub>3b</sub>), 0.96 (3 H, t,  $J = 7.4$  Hz, H<sub>11</sub>), 0.89 (3 H, t,  $J = 7.4$  Hz, H<sub>1</sub>);  $^{13}\text{C}$  NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 174.1 (C<sub>7</sub>), 140.4 (C<sub>13</sub>), 128.9 (C<sub>14</sub>), 128.1 (C<sub>15</sub>), 126.7 (C<sub>16</sub>), 64.1 (C<sub>8</sub>), 56.5 (C<sub>4</sub>), 53.3 (C<sub>12</sub>), 31.8 (C<sub>6</sub>), 30.9 (C<sub>3</sub>), 30.7 (C<sub>9</sub>), 25.5 (C<sub>5</sub>), 20.4 (C<sub>2</sub>), 19.2 (C<sub>10</sub>), 14.3 (C<sub>1</sub>), 13.8 (C<sub>11</sub>);  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  382.2739, C<sub>25</sub>H<sub>36</sub>NO<sub>2</sub>H requires 382.2741.

*tert-butyl 4-(dibenzylamino)heptanoate 667c*

Prepared according to general procedure B using dibenzylamine (39  $\mu\text{L}$ , 0.2 mmol), butyraldehyde (20  $\mu\text{L}$ , 0.22 mmol) and *tert*-butyl acrylate (32  $\mu\text{L}$ , 0.22 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (64 mg, 84%).  $R_f$  (5% ethyl acetate in petroleum ether): 0.44; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film):

2956, 2930, 2871, 1726, 1602, 1494, 1453, 1390, 1365, 1250, 1150, 1073.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.35 (4 H, app d,  $J = 7.2$  Hz,  $\text{H}_{12}$ ), 7.29 (4 H, t,  $J = 7.3$  Hz,  $\text{H}_{13}$ ), 7.21 (2 H, app t,  $J = 7.2$  Hz,  $\text{H}_{14}$ ), 3.65 (2 H, d,  $J = 13.7$  Hz,  $\text{H}_{10a}$ ), 3.49 (2 H, d,  $J = 13.7$  Hz,  $\text{H}_{10b}$ ), 2.47 – 2.36 (2 H, m,  $\text{H}_4$  and  $\text{H}_{6a}$ ), 2.16 (1H, ddd,  $J = 6.4, 9.2, 15.8$  Hz,  $\text{H}_{6b}$ ), 1.85 – 1.76 (1 H, m,  $\text{H}_{5a}$ ), 1.70 – 1.56 (2 H, m,  $\text{H}_{3a}$  and  $\text{H}_{5b}$ ), 1.41 (9 H, s,  $\text{H}_9$ ), 1.34 (2 H, sext,  $J = 7.6$  Hz,  $\text{H}_2$ ), 1.24 – 1.15 (1 H, m,  $\text{H}_{3b}$ ), 0.86 (3 H, t,  $J = 7.4$  Hz,  $\text{H}_1$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 173.6 ( $\text{C}_7$ ), 140.6 ( $\text{C}_{11}$ ), 129.0 ( $\text{C}_{12}$ ), 128.3 ( $\text{C}_{13}$ ), 126.8 ( $\text{C}_{14}$ ), 80.1 ( $\text{C}_8$ ), 56.9 ( $\text{C}_4$ ) 53.5 ( $\text{C}_{10}$ ), 33.3 ( $\text{C}_6$ ), 31.2 ( $\text{C}_3$ ), 28.2 ( $\text{C}_9$ ), 25.6 ( $\text{C}_5$ ), 20.5 ( $\text{C}_2$ ), 14.4 ( $\text{C}_1$ ); m/z HRMS found  $[\text{M} + \text{H}]^+$  382.2741,  $\text{C}_{25}\text{H}_{36}\text{NO}_2$  requires 382.2741.

*benzyl 4-(dibenzylamino)heptanoate* **667d**

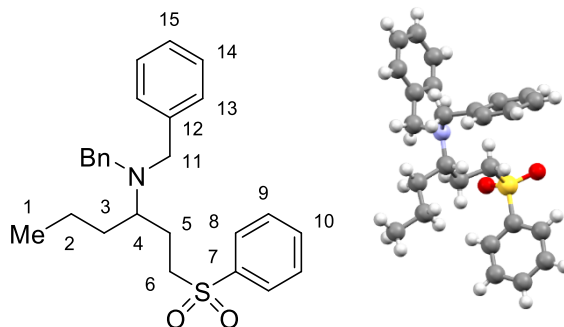


Prepared according to general procedure B using dibenzylamine (39  $\mu\text{L}$ , 0.2 mmol), butyraldehyde (20  $\mu\text{L}$ , 0.22 mmol) and benzyl acrylate (34  $\mu\text{L}$ , 0.22 mmol). The crude reaction mixture was purified by flash column chromatography (0.5%  $\text{Et}_3\text{N}$  in dichloromethane) to afford the product as a colourless oil (70 mg, 84%).  $R_f$  (5% ethyl acetate in petroleum ether): 0.55; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3028, 2955, 2932, 2869, 1732, 1601, 1494, 1453, 1377, 1264, 1208, 1163.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.39 – 7.19 (15 H, m,  $\text{H}_{10}$ ,  $\text{H}_{11}$ ,  $\text{H}_{12}$ ,  $\text{H}_{15}$ ,  $\text{H}_{16}$  and  $\text{H}_{17}$ ), 5.05 (1 H, d,  $J = 12.5$  Hz,  $\text{H}_{8a}$ ), 5.01 (1 H, d,  $J = 12.5$  Hz,  $\text{H}_{8b}$ ), 3.67 (2 H, d,  $J = 13.8$  Hz,  $\text{H}_{13a}$ ), 3.46 (2 H, d,  $J = 13.8$  Hz,  $\text{H}_{13b}$ ), 2.59 – 2.44 (2 H, m,  $\text{H}_4$  and  $\text{H}_{6a}$ ), 2.37 – 2.29 (1 H, m,  $\text{H}_{6b}$ ), 1.87 – 1.78 (1 H, m,  $\text{H}_{5a}$ ), 1.73 – 1.66 (2 H, m,  $\text{H}_{3a}$  and  $\text{H}_{5b}$ ), 1.38 – 1.24 (2 H,  $\text{H}_2$ ), 1.23 – 1.14 (1 H, m,  $\text{H}_{3b}$ ), 0.86 (3 H, t,  $J = 7.3$  Hz,  $\text{H}_1$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 174.0 ( $\text{C}_7$ ), 140.5 ( $\text{C}_{14}$ ), 136.2 ( $\text{C}_9$ ), 129.0 ( $\text{C}_{15}$ ), 128.7 ( $\text{C}_{10}$ ), 128.4 ( $\text{C}_{11}$ ), 128.3 ( $\text{C}_{16}$  and  $\text{C}_{12}$ ), 126.9 ( $\text{C}_{17}$ ), 66.2 ( $\text{C}_8$ ), 56.6 ( $\text{C}_4$ ), 53.4 ( $\text{C}_{13}$ ), 31.9 ( $\text{C}_6$ ), 30.9 ( $\text{C}_3$ ), 25.5 ( $\text{C}_5$ ), 20.5 ( $\text{C}_2$ ), 14.4 ( $\text{C}_1$ ); m/z HRMS found  $[\text{M} + \text{H}]^+$  416.2579,  $\text{C}_{28}\text{H}_{34}\text{NO}_2$  requires 416.2584.

Repeated in a 50 mL Schlenk tube using dibenzylamine (0.77 mL, 4 mmol), butyraldehyde (0.40 mL, 4.4 mmol), benzyl acrylate (0.67 mL, 4.4 mmol), ethyl-HEH (1.52 g, 6 mmol), 4Å MS (2.0 g),

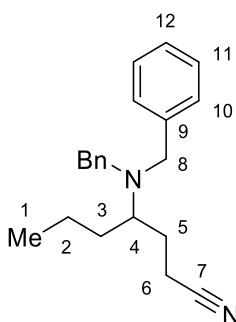
propanoic acid (60  $\mu$ L, 0.8 mmol) and *fac*-Ir(ppy)<sub>3</sub> (13.5 mg, 20  $\mu$ mol, 0.5 mol%) in anhydrous degassed dichloromethane (40 mL). The reaction mixture was irradiated 2.5 h using 2 x 40W Kessil lamps and cooled using 2 desk fans. The crude reaction mixture was filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (1.39 g, 84%).

*N,N*-dibenzyl-1-(phenylsulfonyl)hexan-3-amine **667e**

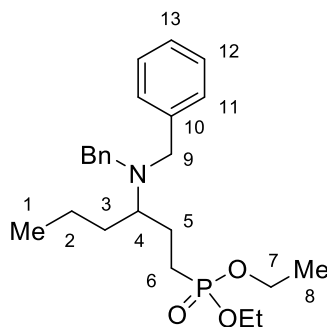


Prepared according to general procedure B using dibenzylamine (39  $\mu$ L, 0.2 mmol), butyraldehyde (20  $\mu$ L, 0.22 mmol) and phenyl vinyl sulfone (37 mg, 0.22 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless crystalline solid (69 mg, 82%). *R<sub>f</sub>* (5% ethyl acetate in petroleum ether): 0.27; m.p. 100 – 102 °C; IR  $\nu_{\text{max}}$ /cm<sup>-1</sup> (film): 3060, 3027, 2956, 2931, 2851, 1601, 1585, 1493, 1450, 1378, 1305, 1281, 1210, 1169, 1140, 1085, 1069. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.83 (2 H, dd, *J* = 1.4, 7.2 Hz, H<sub>8</sub>), 7.62 (1 H, t, *J* = 7.2 Hz, H<sub>10</sub>), 7.52 (2 H, t, *J* = 7.8 Hz, H<sub>9</sub>), 7.30 – 7.20 (10 H, m, H<sub>13</sub>, H<sub>14</sub> and H<sub>15</sub>), 3.58 (2 H, d, *J* = 13.4 Hz, H<sub>11a</sub>), 3.41 (1 H, ddd, *J* = 4.9, 11.1, 14.3 Hz, H<sub>6a</sub>), 3.36 (2 H, d, *J* = 13.4 Hz, H<sub>11b</sub>), 2.82 (1 H, ddd, *J* = 4.9, 11.1, 14.3 Hz, H<sub>6b</sub>), 2.41 (1 H, spt, *J* = 4.7 Hz, H<sub>4</sub>), 1.86 – 1.64 (3 H, m, H<sub>5</sub> and H<sub>3a</sub>), 1.31 – 1.09 (3 H, m, H<sub>2</sub> and H<sub>3b</sub>), 0.84 (3 H, t, *J* = 6.9 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 139.9 (C<sub>12</sub>), 139.3 (C<sub>7</sub>), 133.6 (C<sub>10</sub>), 129.3 (C<sub>9</sub>), 129.0 (C<sub>13</sub>), 128.4 (C<sub>14</sub>), 128.1 (C<sub>8</sub>), 127.1 (C<sub>15</sub>), 56.4 (C<sub>4</sub>), 54.4 (C<sub>6</sub>), 53.3 (C<sub>11</sub>), 30.6 (C<sub>3</sub>), 23.9 (C<sub>5</sub>), 20.5 (C<sub>2</sub>), 14.3 (C<sub>1</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 422.2145, C<sub>26</sub>H<sub>32</sub>NO<sub>2</sub>S requires 422.2148. X-ray structure deposited with the Cambridge Crystallographic Data Centre: CCDC 1819790.

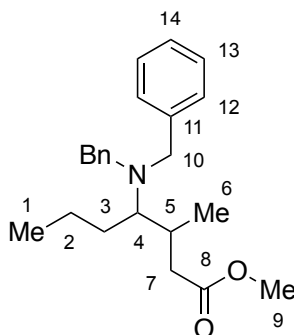


4-(dibenzylamino)heptanenitrile **667f**

Prepared according to general procedure B using dibenzylamine (39  $\mu$ l, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and acrylonitrile (26  $\mu$ L, 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (54 mg, 88%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.48; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3028, 2956, 2933, 2870, 2246, 1696, 1643, 1601, 1542, 1493, 1453, 1423, 1376, 1265, 1142, 1095. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.37 – 7.25 (10 H, m, H<sub>10</sub>, H<sub>11</sub> and H<sub>12</sub>), 3.71 (2 H, d, *J* = 13.6 Hz, H<sub>8a</sub>), 3.46 (2 H, d, *J* = 13.6 Hz, H<sub>8b</sub>), 2.61 – 2.50 (2 H, m, H<sub>4</sub> and H<sub>6a</sub>), 2.16 (1 H, ddd, *J* = 7.2, 8.9, 16.4 Hz, H<sub>6b</sub>), 1.83 – 1.68 (3 H, m, H<sub>3a</sub> and H<sub>5</sub>), 1.45 – 1.19 (3 H, m, H<sub>2</sub> and H<sub>3b</sub>), 0.94 (3 H, t, *J* = 7.3 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 139.9 (C<sub>9</sub>), 129.0 (C<sub>10</sub>), 128.5 (C<sub>11</sub>), 127.2 (C<sub>12</sub>), 120.4 (C<sub>7</sub>), 56.8 (C<sub>4</sub>), 53.6 (C<sub>8</sub>), 30.3 (C<sub>3</sub>), 27.2 (C<sub>5</sub>), 20.6 (C<sub>2</sub>), 14.8 (C<sub>6</sub>), 14.4 (C<sub>1</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 307.2170, C<sub>21</sub>H<sub>27</sub>N<sub>2</sub> requires 307.2169.

*diethyl (3-(dibenzylamino)hexyl)phosphonate 667g*

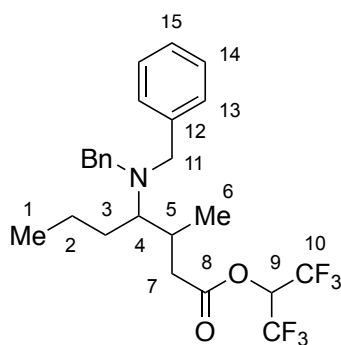
Prepared according to general procedure B using dibenzylamine (39  $\mu\text{L}$ , 0.2 mmol), butyraldehyde (20  $\mu\text{L}$ , 0.22 mmol) and diethyl vinylphosphonate (34  $\mu\text{L}$ , 0.22 mmol). The crude reaction mixture was purified by flash column chromatography (gradient elution: 30% ethyl acetate in petroleum ether to 50% ethyl acetate in petroleum ether) to afford the product as a colourless oil (50 mg, 60%).  $R_f$  (50% ethyl acetate in petroleum ether): 0.21; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2956, 2932, 2870, 1714, 1656, 1602, 1541, 1494, 1453, 1367, 1233, 1164.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.33 – 7.27 (8 H, m,  $\text{H}_{11}$  and  $\text{H}_{12}$ ), 7.21 (2 H, tt,  $J = 1.4, 6.4$  Hz,  $\text{H}_{13}$ ), 4.04 (4 H, m,  $\text{H}_7$ ), 3.66 (2 H, d,  $J = 13.7$  Hz,  $\text{H}_{9a}$ ), 3.46 (2 H, d,  $J = 13.7$  Hz,  $\text{H}_{9b}$ ), 2.44 – 2.38 (1 H, m,  $\text{H}_4$ ), 2.11 – 2.01 (1 H, m,  $\text{H}_{6a}$ ), 1.81 – 1.55 (3 H, m,  $\text{H}_{3a}$  and  $\text{H}_5$ ), 1.51 – 1.41 (1 H, m,  $\text{H}_{6b}$ ), 1.34 – 1.26 (8 H,  $\text{H}_2$  and  $\text{H}_8$ ), 1.23 – 1.18 (1 H, m,  $\text{H}_{3b}$ ), 0.87 (3 H, t,  $J = 7.2$  Hz,  $\text{H}_1$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 140.4 ( $\text{C}_{10}$ ), 129.0 ( $\text{C}_{11}$ ), 128.3 ( $\text{C}_{12}$ ), 126.9 ( $\text{C}_{13}$ ), 61.5 (t,  $J = 6.4$  Hz,  $\text{C}_7$ ), 57.9 (d,  $J = 17.1$  Hz,  $\text{C}_4$ ), 53.4 ( $\text{C}_9$ ), 30.8 ( $\text{C}_3$ ), 23.3 (d,  $J = 140.3$  Hz,  $\text{C}_6$ ), 23.3 (d,  $J = 4.5$  Hz,  $\text{C}_5$ ), 20.6 ( $\text{C}_2$ ), 16.6 (d,  $J = 5.9$  Hz,  $\text{C}_8$ ), 14.4 ( $\text{C}_1$ );  $^{31}\text{P}\{^1\text{H}\}$  NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$ : 33.6;  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  418.2502,  $\text{C}_{24}\text{H}_{37}\text{NO}_3\text{P}$  requires 418.2506.

*methyl 4-(dibenzylamino)-3-methylheptanoate 667j*

Prepared according to general procedure B using dibenzylamine (39  $\mu\text{L}$ , 0.2 mmol), butyraldehyde (36  $\mu\text{L}$ , 0.4 mmol) and methyl crotonate (42  $\mu\text{L}$ , 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (0.5%  $\text{Et}_3\text{N}$  in dichloromethane) to afford the product as a

colourless oil (29.8 mg, 42%, 1:1 d.r.).  $R_f$  (10% ethyl acetate in petroleum ether): 0.58; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 3025, 2957, 2870, 2798, 1734, 1602, 1494, 1453, 1435, 1359, 1283, 1247, 1171.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.36 – 7.19 (10 H, m,  $\text{H}_{12}$ ,  $\text{H}_{13}$  and  $\text{H}_{14}$ ), 3.72 (2 H, dd,  $J = 2.3, 13.7$  Hz,  $\text{H}_{10a}$ ), [3.62 (s), 3.58 (s) total 3 H,  $\text{H}_9$ ], 3.50 (2 H, d,  $J = 13.7$  Hz,  $\text{H}_{10b}$ ), [2.93 (d,  $J = 15.0$  Hz), 2.92 (d,  $J = 15.5$  Hz), 1.84 (d,  $J = 15.0$  Hz), 1.81 (d,  $J = 15.0$  Hz) total 1 H,  $\text{H}_{7a}$ ], [2.33 (d,  $J = 15.0$  Hz), 2.32 (d,  $J = 15.0$  Hz), 2.10 (d,  $J = 15.0$  Hz), 2.08 (d,  $J = 15.1$  Hz) total 1 H,  $\text{H}_{7b}$ ], [2.47 (q,  $J = 6.0$  Hz), 2.28 – 2.17 (m) total 1 H,  $\text{H}_4$ ], 2.28 – 2.17 (1 H, m,  $\text{H}_5$ ), 1.72 – 1.62 (1 H, m,  $\text{H}_{3a}$ ), 1.44 – 1.27 (3 H, m,  $\text{H}_2$  and  $\text{H}_{3b}$ ), [0.96 (d,  $J = 6.9$  Hz), 0.89 (d,  $J = 6.3$  Hz) total 3 H,  $\text{H}_6$ ], 0.91 (3 H, t,  $J = 7.2$  Hz,  $\text{H}_1$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : [174.6, 174.2 ( $\text{C}_8$ )], [140.5, 140.4 ( $\text{C}_{11}$ )], 129.2 ( $\text{C}_{12}$ ), 128.3 ( $\text{C}_{13}$ ), [126.9, 126.9 ( $\text{C}_{14}$ )], [61.3, 61.5 ( $\text{C}_4$ )], [55.2, 54.2 ( $\text{C}_{10}$ )], [51.5, 51.5 ( $\text{C}_9$ )], [39.9, 39.3 ( $\text{C}_7$ )], [32.7, 32.0 ( $\text{C}_5$ )], [29.4, 28.7 ( $\text{C}_3$ )], [22.5, 21.7 ( $\text{C}_2$ )], [17.6, 17.2 ( $\text{C}_6$ )], [14.8, 14.6 ( $\text{C}_1$ )];  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  354.2432,  $\text{C}_{23}\text{H}_{32}\text{NO}_2$  requires 354.2428.

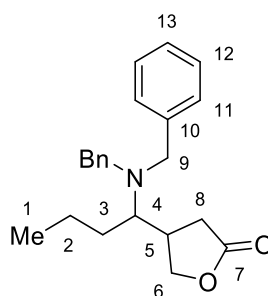
**1,1,1,3,3,3-hexafluoropropan-2-yl 4-(dibenzylamino)-3-methylheptanoate 667k**



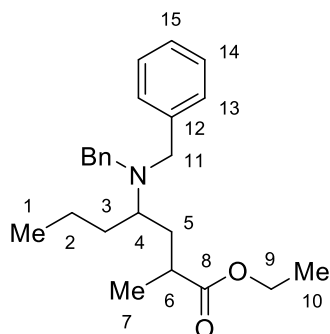
Prepared according to general procedure B using dibenzylamine (39  $\mu\text{L}$ , 0.2 mmol), butyraldehyde (36  $\mu\text{L}$ , 0.4 mmol) and 1,1,1,3,3,3-hexafluoropropan-2-yl crotonate (94 mg, 0.4 mmol). The crude reaction mixture was purified twice by flash column chromatography (0.5%  $\text{Et}_3\text{N}$  in dichloromethane) and subsequently (20%  $\text{PhCF}_3$  in petroleum ether) to afford the product as a colourless oil (65.9 mg, 67%, 1:1 d.r.).  $R_f$  (10% ethyl acetate in petroleum ether): 0.88; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 3030, 2960, 2932, 1775, 1603, 1495, 1454, 1385, 1354, 1288, 1266, 1225, 1198, 1169, 1107.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.35 – 7.22 (10 H, m,  $\text{H}_{13}$ ,  $\text{H}_{14}$  and  $\text{H}_{15}$ ), [5.78 (spt,  $J = 6.1$  Hz), 5.74 (spt,  $J = 6.1$  Hz) total 1 H,  $\text{H}_9$ ], [3.75 (d,  $J = 13.0$  Hz), 3.73 (d,  $J = 17.7$  Hz) total 2 H,  $\text{H}_{11a}$ ], [3.53 (d,  $J = 13.5$  Hz), 3.46 (d,  $J = 13.5$  Hz) total 2 H,  $\text{H}_{11b}$ ], [3.28 (d,  $J = 14.9$  Hz), 3.28 (d,  $J = 14.9$  Hz), 1.90 – 1.84 (m) total 1 H,  $\text{H}_{7a}$ ], [2.50 (q,  $J = 5.6$  Hz), 2.26 – 2.20 (m) total 1 H,  $\text{H}_4$ ], [2.43 (d,  $J = 15.0$  Hz), 2.42 (d,  $J = 15.1$  Hz), 2.33 (d,  $J = 15.0$  Hz), 2.30 (d,  $J = 15.1$  Hz) total 1 H,  $\text{H}_{7b}$ ], 2.26 – 2.20 (1 H, m,  $\text{H}_5$ ), 1.77 – 1.63 (1 H, m,  $\text{H}_{3a}$ ), 1.48 – 1.31 (3 H, m,  $\text{H}_2$  and  $\text{H}_{3b}$ ), [0.99 (d,  $J = 6.6$  Hz), 0.90 (d,  $J =$

6.5 Hz) total 3 H, H<sub>6</sub>], [0.95 (t,  $J = 7.0$  Hz), 0.92 (t,  $J = 7.0$  Hz) total 3 H, H<sub>1</sub>]; <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : [171.0, 170.5 (C<sub>8</sub>)], [140.2, 140.0 (C<sub>11</sub>)], [129.2, 129.1 (C<sub>12</sub>)], [128.4, 128.4 (C<sub>13</sub>)], 127.1 (C<sub>14</sub>), 120.6 (q,  $J = 281$  Hz, C<sub>10</sub>), [66.4 (app qt,  $J = 34.8$  Hz), 66.3 (app qt,  $J = 34.8$  Hz), C<sub>9</sub>], [61.5, 61.0 (C<sub>4</sub>)], [55.1, 54.4 (C<sub>10</sub>)], [39.0, 38.7 (C<sub>7</sub>)], [33.5, 32.4 (C<sub>5</sub>)], [29.6, 29.0 (C<sub>3</sub>)], [22.7, 21.7 (C<sub>2</sub>)], [17.1, 16.9 (C<sub>6</sub>)], [14.8, 14.6 (C<sub>1</sub>)]. <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$ : -74.1 – -74.2 (m), -74.2 (s); m/z HRMS found [M + H]<sup>+</sup> 490.2165, C<sub>25</sub>H<sub>30</sub>F<sub>6</sub>NO<sub>2</sub> requires 490.2175.

**4-(1-(dibenzylamino)butyl)dihydrofuran-2(3H)-one 667n**



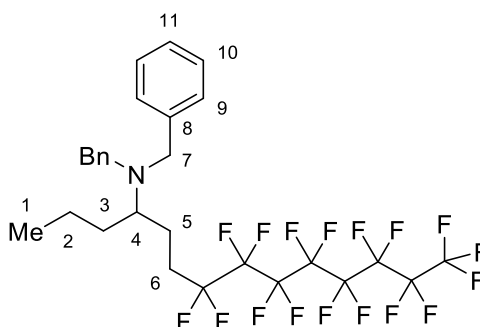
Prepared according to general procedure B using dibenzylamine (39  $\mu$ L, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and 2-furanone (28  $\mu$ L, 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (30 mg, 46%, 1:1 d.r.). R<sub>f</sub> (10% ethyl acetate in petroleum ether): 0.25; IR  $\nu_{\text{max}}$ /cm<sup>-1</sup> (film): 2957, 2931, 2870, 1773, 1601, 1493, 1453, 1417, 1366, 1306, 1249, 1169, 1110, 1067, 1015. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.35 – 7.26 (10 H, m, H<sub>11</sub>, H<sub>12</sub> and H<sub>13</sub>), [4.54 (t,  $J = 8.7$  Hz), 4.31 (t,  $J = 8.2$  Hz) total 1 H, H<sub>6a</sub>], [3.83 (t,  $J = 9.5$  Hz), 3.81 (t,  $J = 9.0$  Hz), total 1 H, H<sub>6b</sub>], [3.73 (d,  $J = 13.5$  Hz), 3.72 (d,  $J = 13.6$  Hz), total 2 H, H<sub>9a</sub>], [3.54 (d,  $J = 13.6$  Hz), 3.50 (d,  $J = 13.5$  Hz), total 2 H, H<sub>9b</sub>], 2.81 – 2.73 (1 H, m, H<sub>5</sub>), [2.71 (dd,  $J = 7.7, 16.9$  Hz), 2.47 (dd,  $J = 8.2, 16.9$  Hz), 2.33 (d,  $J = 10.1, 17.3$  Hz), 2.11 (d,  $J = 11.1, 17.4$  Hz) total 1 H, H<sub>8</sub>], 2.58 – 2.54 (1 H, m, H<sub>4</sub>), [1.83 – 1.72 (m), 1.24 – 1.17 (m), total 2 H, H<sub>3</sub>], 1.52 – 1.26 (2 H, m, H<sub>2</sub>), [0.96 (t,  $J = 7.4$  Hz), 0.94 (t,  $J = 7.3$  Hz), total 3 H, H<sub>1</sub>]; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : [177.3, 177.1 (C<sub>7</sub>)], [139.6, 139.5 (C<sub>10</sub>)], 129.0 (C<sub>11</sub>), 128.6 (C<sub>12</sub>), [127.4, 127.4 (C<sub>13</sub>)], [73.4, 71.6 (C<sub>6</sub>)], [60.6, 60.0 (C<sub>4</sub>)], [54.3, 54.3 (C<sub>9</sub>)], [40.0, 39.4 (C<sub>5</sub>)], [34.2, 33.5 (C<sub>8</sub>)], [31.3, 31.3 (C<sub>3</sub>)], [21.8, 21.5 (C<sub>2</sub>)], [14.8, 14.8 (C<sub>1</sub>)]; m/z HRMS found [M + H]<sup>+</sup> 338.2116, C<sub>22</sub>H<sub>28</sub>NO<sub>2</sub> requires 338.2126.

ethyl 4-(dibenzylamino)-2-methylheptanoate **667s**

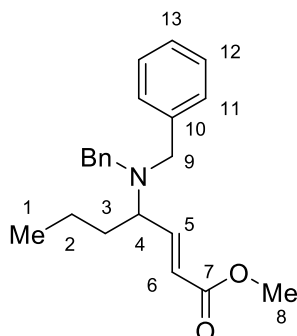
Prepared according to general procedure B using dibenzylamine (39  $\mu\text{L}$ , 0.2 mmol), butyraldehyde (20  $\mu\text{L}$ , 0.22 mmol) and ethyl methacrylate (27  $\mu\text{L}$ , 0.22 mmol). The crude reaction mixture was purified by flash column chromatography (0.5%  $\text{Et}_3\text{N}$  in dichloromethane) to afford the product as a colourless oil (58 mg, 80%, 2.3:1 d.r.).  $R_f$  (10% ethyl acetate in petroleum ether): 0.73; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2956, 2932, 2871, 1728, 1601, 1494, 1453, 1375, 1255, 1177, 1148.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.35 – 7.26 (8 H, m,  $\text{H}_{13}$  and  $\text{H}_{14}$ ), 7.21 (2 H, t,  $J = 7.2$  Hz,  $\text{H}_{15}$ ), [4.05 (dq,  $J = 2.0, 7.2$  Hz, major), 3.99 – 3.86 (m, minor), total 2 H,  $\text{H}_9$ ], [3.64 (d,  $J = 13.1$  Hz, major), 3.61 (d,  $J = 13.5$  Hz, minor), total 2 H,  $\text{H}_{11a}$ ], [3.50 (d,  $J = 13.8$  Hz, minor), 3.44 (d,  $J = 13.3$  Hz, major), total 2 H,  $\text{H}_{11b}$ ], 2.70 (1 H, quint,  $J = 7.3$  Hz,  $\text{H}_6$ ), [2.57 – 2.51 (m, minor), 2.49 – 2.42 (m, major), total 1 H,  $\text{H}_4$ ], [1.98 (ddd,  $J = 5.4, 8.4, 13.8$  Hz, major,  $\text{H}_{5a'}$ ), 1.73 – 1.62 (m, minor,  $\text{H}_{5a''}$ ), 1.49 (ddd,  $J = 5.3, 8.1, 13.5$  Hz, minor,  $\text{H}_{5b'}$ ), 1.39 – 1.22 (m, major,  $\text{H}_{5b''}$ ) total 2 H], 1.73 – 1.62 (2 H, m,  $\text{H}_3$ ), 1.39 – 1.22 (2 H, m,  $\text{H}_2$ ), 1.20 – 1.13 (3 H, m,  $\text{H}_{10}$ ), [1.09 (d,  $J = 7.3$  Hz, minor), 0.79 (d,  $J = 6.9$  Hz, major), total 3 H,  $\text{H}_7$ ], 0.86 (3 H, t,  $J = 7.4$  Hz,  $\text{H}_1$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 177.6 ( $\text{C}_8$ , major), 176.9 ( $\text{C}_8$ , minor), 140.6 ( $\text{C}_{12}$ ), 129.3 ( $\text{C}_{13}$ , major), 129.0 ( $\text{C}_{13}$ , minor), 128.2 ( $\text{C}_{14}$ , minor), 128.1 ( $\text{C}_{14}$ , major), 126.9 ( $\text{C}_{15}$ , major), 126.8 ( $\text{C}_{15}$ , minor), 60.2 ( $\text{C}_9$ , major), 60.1 ( $\text{C}_9$ , minor), 55.4 ( $\text{C}_4$ , minor), 54.3 ( $\text{C}_4$ , major), 53.7 ( $\text{C}_{11}$ , minor), 53.3 ( $\text{C}_{11}$ , major), 36.6 ( $\text{C}_6$ , minor), 36.2 ( $\text{C}_6$ , major), 34.6 ( $\text{C}_5$ , major), 34.3 ( $\text{C}_5$ , minor), 31.2 ( $\text{C}_3$ , minor), 31.0 ( $\text{C}_3$ , major), 20.4 ( $\text{C}_2$ , major), 20.3 ( $\text{C}_2$ , minor), 18.4 ( $\text{C}_7$ , major), 16.5 ( $\text{C}_7$ , minor), 14.4 – 14.2 ( $\text{C}_1$  and  $\text{C}_{10}$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  368.2585,  $\text{C}_{24}\text{H}_{34}\text{NO}_2$  requires 368.2582.

*N,N*-dibenzyl-7,7,8,8,9,9,10,10,11,11,12,12,13,13,14,14,14-heptafluorotetradecan-4-amine

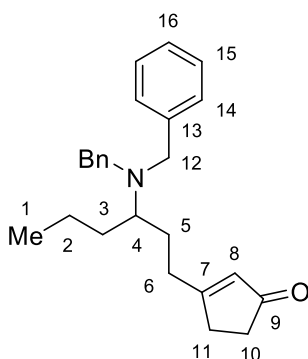
**667aa**



Prepared according to general procedure B using dibenzylamine (39  $\mu$ L, 0.2 mmol), butyraldehyde (20  $\mu$ L, 0.22 mmol) and 1*H*, 1*H*, 2*H*-perfluoro-1-decene (68  $\mu$ L, 0.22 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (112 mg, 80%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.94; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2961, 1495, 1455, 1363, 1237, 1202, 1145, 1112, 1063, 1028. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.33 – 7.21 (10 H, m, H<sub>9</sub>, H<sub>10</sub> and H<sub>11</sub>), 3.69 (2 H, d, *J* = 13.7 Hz, H<sub>7a</sub>), 3.44 (2 H, d, *J* = 13.7 Hz, H<sub>7b</sub>), 2.49 – 2.42 (2 H, m, H<sub>4</sub> and H<sub>6a</sub>), 1.79 – 1.68 (3 H, m, H<sub>3a</sub>, H<sub>5a</sub> and H<sub>6b</sub>), 1.64 – 1.55 (1 H, m, H<sub>5b</sub>), 1.41 – 1.18 (3 H, m, H<sub>2</sub> and H<sub>3b</sub>), 0.91 (3 H, t, *J* = 7.3 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 140.2 (C<sub>8</sub>), 129.1 (C<sub>9</sub>), 128.4 (C<sub>10</sub>), 127.1 (C<sub>11</sub>), 121.9 – 121.2 (m), 119.2 – 118.4 (m), 116.7 – 115.5 (m), 114.3 – 112.7 (m), 112.0 – 110.1 (m), 109.1 – 107.4 (m), 106.5 – 105.3 (m), 56.8 (C<sub>4</sub>), 53.4 (C<sub>7</sub>), 30.8 (C<sub>3</sub>), 28.9 (t, *J* = 21.9 Hz, C<sub>6</sub>), 21.1 (C<sub>5</sub>), 20.7 (C<sub>2</sub>), 14.4 (C<sub>1</sub>); <sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$ : –80.8 (t, *J* = 10.0 Hz), –114.2 (t, *J* = 12.8 Hz), –121.7 (br m), –121.9 (br m), –122.7 (br m), –123.7 (br m), –126.1 (br m); *m/z* HRMS found [M + H]<sup>+</sup> 700.1898, C<sub>28</sub>H<sub>27</sub>F<sub>17</sub>N requires 700.1867.

*methyl (E)-4-(dibenzylamino)hept-2-enoate 667ab*

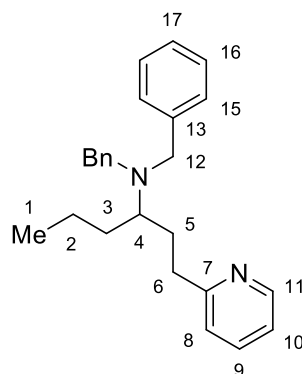
Prepared according to general procedure B using dibenzylamine (39  $\mu\text{L}$ , 0.2 mmol), butyraldehyde (36  $\mu\text{L}$ , 0.4 mmol) and methyl propiolate (35  $\mu\text{L}$ , 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (0.5%  $\text{Et}_3\text{N}$  in dichloromethane) to afford the product as a colourless oil (44.2 mg, 66%).  $R_f$  (10% ethyl acetate in petroleum ether): 0.60; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2955, 2931, 2872, 1722, 1651, 1602, 1494, 1453, 1434, 1364, 1269, 1223, 1171, 1139.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.37 (4 H, d,  $J = 7.3$  Hz,  $\text{H}_{11}$ ), 7.31 (4 H, t,  $J = 7.1$  Hz,  $\text{H}_{12}$ ), 7.23 (2 H, tt,  $J = 1.6, 7.1$  Hz,  $\text{H}_{13}$ ), 6.99 (1 H, dd,  $J = 8.6, 15.8$  Hz,  $\text{H}_5$ ), 5.84 (1 H, dd,  $J = 0.9, 15.8$  Hz,  $\text{H}_6$ ), 3.83 (2 H, d,  $J = 13.8$  Hz,  $\text{H}_{9a}$ ), 3.78 (3 H, s,  $\text{H}_8$ ), 3.41 (2 H, d,  $J = 13.8$  Hz,  $\text{H}_{9b}$ ), 3.19 (1 H, q,  $J = 6.9$  Hz,  $\text{H}_4$ ), 1.79 – 1.64 (1 H, m,  $\text{H}_{3a}$ ), 1.49 – 1.26 (3 H, m,  $\text{H}_2$  and  $\text{H}_{3b}$ ), 0.82 (3 H, t,  $J = 7.1$  Hz,  $\text{H}_1$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 166.9 ( $\text{C}_7$ ), 147.8 ( $\text{C}_5$ ), 140.0 ( $\text{C}_{10}$ ), 128.7 ( $\text{C}_{11}$ ), 128.4 ( $\text{C}_{12}$ ), 127.0 ( $\text{C}_{13}$ ), 123.1 ( $\text{C}_6$ ), 58.8 ( $\text{C}_4$ ), 53.8 ( $\text{C}_9$ ), 51.7 ( $\text{C}_8$ ), 33.6 ( $\text{C}_3$ ), 19.7 ( $\text{C}_2$ ), 14.1 ( $\text{C}_1$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  338.2117,  $\text{C}_{22}\text{H}_{28}\text{NO}_2$  requires 338.2115.

*3-(3-(dibenzylamino)hexyl)cyclopent-2-en-1-one 667ad*

Prepared according to general procedure B using dibenzylamine (39  $\mu\text{L}$ , 0.2 mmol), butyraldehyde (36  $\mu\text{L}$ , 0.4 mmol) and 3-vinylcyclopent-2-en-1-one **666ad** (48 mg, 0.4 mmol). The crude reaction

mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (23 mg, 24%). *R<sub>f</sub>* (20% ethyl acetate in petroleum ether): 0.29; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2926, 2869, 1704, 1673, 1613, 1493, 1452, 1363, 1246, 1184, 1142. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.34 – 7.20 (10 H, m, H<sub>14</sub>, H<sub>15</sub> and H<sub>16</sub>), 5.77 (1 H, t, *J* = 1.4 Hz, H<sub>8</sub>), 3.66 (2 H, d, *J* = 13.6 Hz, H<sub>12a</sub>), 3.48 (2 H, d, *J* = 13.6 Hz, H<sub>12b</sub>), 2.57 – 2.42 (4 H, m, H<sub>4</sub>, H<sub>6a</sub> and H<sub>11</sub>), 2.38 – 2.28 (3 H, m, H<sub>6b</sub> and H<sub>10</sub>), 1.79 – 1.67 (2 H, m, H<sub>3a</sub> and H<sub>5a</sub>), 1.61 – 1.52 (1 H, m, H<sub>5b</sub>), 1.38 – 1.28 (2 H, m, H<sub>2</sub>), 1.25 – 1.16 (1 H, m, H<sub>3b</sub>), 0.89 (3 H, t, *J* = 7.3 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 210.2 (C<sub>9</sub>), 183.7 (C<sub>7</sub>), 140.4 (C<sub>13</sub>), 129.2 (C<sub>8</sub>), 129.1 (C<sub>14</sub>), 128.3 (C<sub>15</sub>), 127.0 (C<sub>16</sub>), 56.7 (C<sub>4</sub>), 53.6 (C<sub>12</sub>), 35.3 (C<sub>10</sub>), 31.8 (C<sub>11</sub>), 31.1 (C<sub>3</sub>), 31.0, (C<sub>6</sub>), 27.9 (C<sub>5</sub>), 20.7 (C<sub>2</sub>), 14.5 (C<sub>1</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 362.2480, C<sub>25</sub>H<sub>32</sub>NO requires 362.2478.

*N,N*-dibenzyl-1-(pyridin-2-yl)hexan-3-amine **667ah**

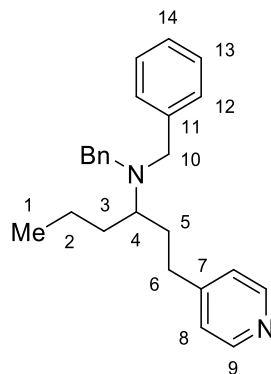


Prepared according to general procedure B using dibenzylamine (39  $\mu$ L, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and 2-vinylpyridine (43  $\mu$ L, 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (27 mg, 37%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.28; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2954, 2929, 2869, 2800, 1589, 1568, 1493, 1473, 1453, 1433, 1362, 1245, 1205, 1146, 1099, 1062, 1050, 1027. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.52 (1 H, d, *J* = 4.6 Hz, H<sub>11</sub>), 7.50 (1 H, dt, *J* = 1.8, 7.7 Hz, H<sub>9</sub>), 7.34 (4 H, d, *J* = 7.1 Hz, H<sub>15</sub>), 7.28 (4 H, t, *J* = 7.2 Hz, H<sub>16</sub>), 7.21 (2 H, dt, *J* = 1.8, 7.1 Hz, H<sub>17</sub>), 7.07 (1 H, dd, *J* = 5.0, 6.7 Hz, H<sub>10</sub>), 6.93 (1 H, d, *J* = 7.8 Hz, H<sub>8</sub>), 3.62 (2 H, d, *J* = 13.7 Hz, H<sub>12a</sub>), 3.55 (2 H, d, *J* = 13.7 Hz, H<sub>12b</sub>), 2.92 (1 H, ddd, *J* = 6.1, 9.8, 13.8 Hz, H<sub>6a</sub>), 2.69 (1 H, ddd, *J* = 5.7, 9.9, 13.8 Hz, H<sub>6b</sub>), 2.52 (1 H, quint, *J* = 6.7 Hz, H<sub>4</sub>), 2.07 – 1.98 (1 H, m, H<sub>5a</sub>), 1.76 – 1.63 (2 H, m, H<sub>3a</sub> and H<sub>5b</sub>), 1.38 – 1.24 (3 H, m, H<sub>3b</sub> and H<sub>2</sub>), 0.81 (3 H, t, *J* = 7.0 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 162.7 (C<sub>7</sub>), 149.4 (C<sub>11</sub>), 140.8 (C<sub>13</sub>), 136.3 (C<sub>9</sub>), 129.1 (C<sub>15</sub>), 128.2 (C<sub>16</sub>), 126.8

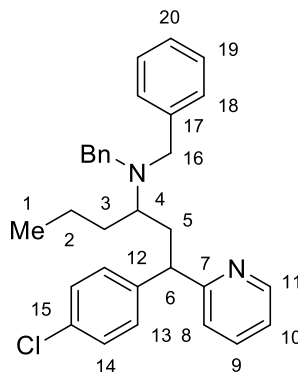


(C<sub>17</sub>), 122.9 (C<sub>8</sub>), 120.9 (C<sub>10</sub>), 56.7 (C<sub>4</sub>), 53.5 (C<sub>12</sub>), 36.1 (C<sub>6</sub>), 31.7 (C<sub>3</sub>), 30.3 (C<sub>5</sub>), 20.4 (C<sub>2</sub>), 14.4 (C<sub>1</sub>); m/z HRMS found [M + H]<sup>+</sup> 359.2491, C<sub>25</sub>H<sub>31</sub>N<sub>2</sub> requires 359.2482.

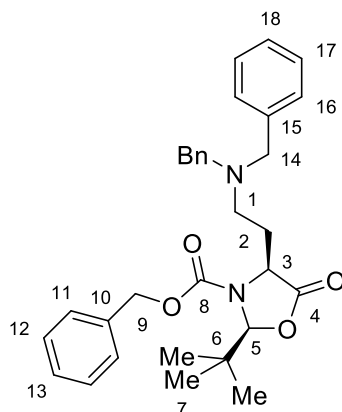
*N,N*-dibenzyl-1-(pyridin-4-yl)hexan-3-amine **667ai**



Prepared according to general procedure B using dibenzylamine (39  $\mu$ l, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and 4-vinylpyridine (43  $\mu$ L, 0.4 mmol). The crude reaction mixture was filtered, the solvent removed *in vacuo* and subsequently dissolved in a solution of lithium hydroxide monohydrate (84 mg, 20 mmol) in tetrahydrofuran/water (6 mL, 5:1). The mixture was heated to a vigorous reflux for 2 hours, cooled to room temperature and diluted with saturated aqueous NaHCO<sub>3</sub> (10 mL). The aqueous was extracted with ethyl acetate (3 x 10 mL) and the organic combined and washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent removed *in vacuo*. The subsequent residue was purified by flash column chromatography (gradient elution: 20% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether) to afford the product as a colourless oil (32 mg, 45%). R<sub>f</sub> (30% ethyl acetate in petroleum ether): 0.22; IR  $\nu_{\text{max}}$ /cm<sup>-1</sup> (film): 3027, 2932, 2868, 1643, 1601, 1557, 1493, 1453, 1414, 1363, 1265, 1218, 1142, 1069, 1027. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.42 (2 H, d, *J* = 5.8 Hz, H<sub>9</sub>), 7.35 – 7.29 (8 H, m, H<sub>12</sub> and H<sub>13</sub>), 7.24 (2 H, dt, *J* = 1.6, 6.0 Hz, H<sub>14</sub>), 6.93 (2 H, d, *J* = 6.0 Hz, H<sub>8</sub>), 3.64 (2 H, d, *J* = 13.7 Hz, H<sub>10a</sub>), 3.53 (2 H, d, *J* = 13.7 Hz, H<sub>10b</sub>), 2.76 (1 H, ddd, *J* = 5.9, 9.5, 14.5 Hz, H<sub>6a</sub>), 2.52 – 2.44 (2 H, m, H<sub>4</sub> and H<sub>6b</sub>), 1.88 – 1.81 (1 H, m, H<sub>5a</sub>), 1.72 – 1.66 (1 H, m, H<sub>3a</sub>), 1.60 – 1.53 (1 H, m, H<sub>5b</sub>), 1.33 – 1.22 (3 H, m, H<sub>2</sub> and H<sub>3b</sub>), 0.84 (3 H, t, *J* = 7.0 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 152.1 (C<sub>7</sub>), 149.7 (C<sub>9</sub>), 140.6 (C<sub>11</sub>), 129.1 (C<sub>12</sub>), 128.3 (C<sub>13</sub>), 126.9 (C<sub>14</sub>), 124.0 (C<sub>8</sub>), 56.6 (C<sub>4</sub>), 53.6 (C<sub>10</sub>), 32.8 (C<sub>6</sub>), 31.4 (C<sub>5</sub>), 31.2 (C<sub>3</sub>), 20.5 (C<sub>2</sub>), 14.4 (C<sub>1</sub>); m/z HRMS found [M + H]<sup>+</sup> 359.2492, C<sub>25</sub>H<sub>31</sub>N<sub>2</sub> requires 359.2482.

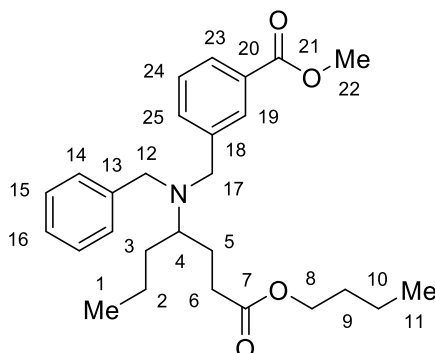
*N,N*-dibenzyl-1-(4-chlorophenyl)-1-(pyridin-2-yl)hexan-3-amine **667ak**

Prepared according to general procedure B using dibenzylamine (39  $\mu$ l, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and 2-(1-(4-chlorophenyl)vinyl)pyridine **666ak** (86 mg, 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (86 mg, 75%, 2.3:1 d.r.). *R*<sub>f</sub> (10% ethyl acetate in petroleum ether): 0.40; IR  $\nu_{\text{max}}$ /cm<sup>-1</sup> (film): 3027, 2955, 2928, 2869, 2801, 1587, 1568, 1489, 1469, 1453, 1432, 1408, 1362, 1245, 1144, 1090, 1027, 1014. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ : [8.58 (d, *J* = 4.8 Hz, minor), 8.52 (d, *J* = 4.8 Hz, major) total 1 H, H<sub>11</sub>], [7.51 (t, *J* = 7.7 Hz, minor), 7.39 (t, *J* = 7.4 Hz, major), total 1 H, H<sub>9</sub>], [7.28 – 7.18 (m), 7.08 (d, *J* = 8.0 Hz, major), 7.06 (d, *J* = 4.5 Hz, minor), 7.03 – 7.01 (m), 6.94 (d, *J* = 8.2 Hz, minor), 6.91 (d, *J* = 7.8 Hz, major), 6.73 (d, *J* = 7.8 Hz, major), total 16 H, H<sub>8</sub>, H<sub>10</sub>, H<sub>13</sub>, H<sub>14</sub>, H<sub>18</sub>, H<sub>19</sub>, H<sub>20</sub>], 4.16 (1 H, t, *J* = 6.8 Hz, H<sub>6</sub>), [3.65 (d, *J* = 13.6 Hz, minor), 3.56 (d, *J* = 13.6 Hz, major) total 2 H, H<sub>16a</sub>], [3.51 (d, *J* = 13.7 Hz, major), 3.47 (d, *J* = 13.5 Hz, minor), total 2 H, H<sub>16b</sub>], [2.49 (app quint, *J* = 6.7 Hz, minor), 2.32 – 2.28 (m, major), 2.21 (app quint, *J* = 6.7 Hz, major), 2.02 (ddd, *J* = 5.0, 8.4, 13.4 Hz, minor), total 2 H, H<sub>5</sub>], 2.39 – 2.34 (1 H, m, H<sub>4</sub>), [1.71 – 1.62 (m, major), 1.35 – 1.25 (m, minor) total 2 H, H<sub>3</sub>], 1.35 – 1.25 (2 H, m, H<sub>2</sub>), 0.75 (3 H, t, *J* = 7.1 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 163.9 (C<sub>7</sub>, minor), 163.0 (C<sub>7</sub>, major), 149.6 (C<sub>11</sub>, minor), 149.4 (C<sub>11</sub>, major), 143.2 (C<sub>12</sub>, major), 142.6 (C<sub>12</sub>, minor), 140.8 (C<sub>17</sub>, minor), 140.6 (C<sub>17</sub>, major), 136.5 (C<sub>9</sub>, minor), 136.3 (C<sub>9</sub>, major), 132.1 (C<sub>15</sub>, major), 131.8 (C<sub>15</sub>, minor), [129.6, 129.3, 129.1, 128.7, 128.4, 128.2 (multiple C) (C<sub>13</sub>, C<sub>14</sub>, C<sub>18</sub>, C<sub>19</sub>)], 126.8 (C<sub>20</sub>, minor), 126.7 (C<sub>20</sub>, major), 123.4 (C<sub>8</sub>, major), 123.1 (C<sub>8</sub>, minor), 121.4 (C<sub>10</sub>, minor), 121.3 (C<sub>10</sub>, major), 54.9 (C<sub>4</sub>, minor), 54.7 (C<sub>4</sub>, major), 53.6 (C<sub>16</sub>, minor), 53.6 (C<sub>16</sub>, major), 49.8 (C<sub>6</sub>, major), 49.7 (C<sub>6</sub>, minor), 36.3 (C<sub>5</sub>, minor), 36.1 (C<sub>5</sub>, major), 31.4 (C<sub>3</sub>, major), 31.0 (C<sub>3</sub>, minor), 20.2 (C<sub>2</sub>, minor), 20.1 (C<sub>2</sub>, major), 14.2 (C<sub>1</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 469.2409 {<sup>35</sup>Cl}, C<sub>31</sub>H<sub>34</sub>N<sub>2</sub>Cl requires 469.2405 {<sup>35</sup>Cl}.

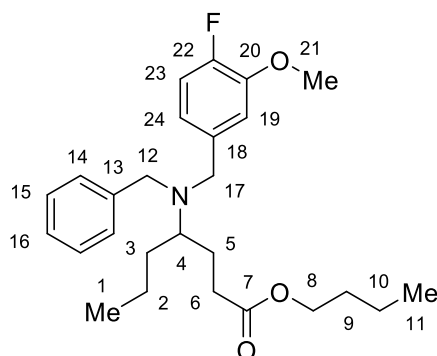
*(2S,4S)*-2-(*tert*-butyl)-3-Cbz-4-(2-(*dibenzylamino*)ethyl)oxazolidin-5-one **670**

Prepared according to general procedure C using dibenzylamine (39  $\mu$ L, 0.2 mmol), paraformaldehyde (30 mg, 1.0 mmol) and (*S*)-2-(*tert*-butyl)-3-Cbz-4-methyleneoxazolidin-5-one **668** (62 mg, 0.22 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (57 mg, 56%, d.r. >20:1). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.34; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2963, 2795, 1790, 1716, 1601, 1494, 1481, 1453, 1390, 1331, 1299, 1227, 1194, 1116, 1071, 1044, 1028, 1006. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.35 – 7.22 (15 H, m, H<sub>11</sub>, H<sub>12</sub>, H<sub>13</sub>, H<sub>16</sub>, H<sub>17</sub> and H<sub>18</sub>), 5.53 (1 H, s, H<sub>5</sub>), 5.13 (1 H, d, *J* = 12.2 Hz, H<sub>9a</sub>), 5.03 (1 H, d, *J* = 11.9 Hz, H<sub>9b</sub>), 4.38 (1 H, t, *J* = 7.4 Hz, H<sub>3</sub>), 3.66 (2 H, d, *J* = 13.7 Hz, H<sub>14a</sub>), 3.47 (2 H, d, *J* = 13.7 Hz, H<sub>14b</sub>), 2.80 – 2.75 (1 H, m, H<sub>1a</sub>), 2.70 – 2.65 (1 H, m, H<sub>1b</sub>), 2.14 – 1.99 (2 H, m, H<sub>2</sub>), 0.91 (9 H, s, H<sub>7</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 172.7 (C<sub>4</sub>), 155.9 (C<sub>8</sub>), 139.3 (C<sub>15</sub>), 135.5 (C<sub>10</sub>), 129.0 (C<sub>16</sub>), 128.8 (C<sub>11</sub>), 128.7 (C<sub>13</sub>), 128.6 (C<sub>12</sub>), 128.3 (C<sub>17</sub>), 127.0 (C<sub>18</sub>), 96.4 (C<sub>5</sub>), 68.3 (C<sub>9</sub>), 58.1 (C<sub>14</sub>), 55.3 (C<sub>3</sub>), 50.1 (C<sub>1</sub>), 37.0 (C<sub>6</sub>), 31.3 (C<sub>2</sub>), 25.0 (C<sub>7</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 501.2746, C<sub>31</sub>H<sub>37</sub>N<sub>2</sub>O<sub>4</sub> requires 501.2748.

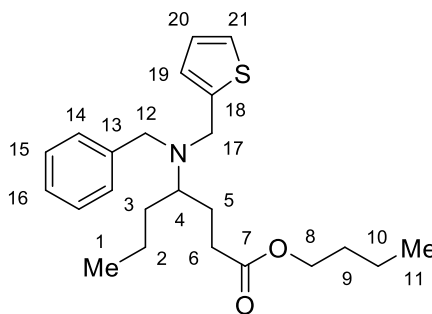
*methyl 3-((benzyl(1-butoxy-1-oxoheptan-4-yl)amino)methyl)benzoate* **672a**



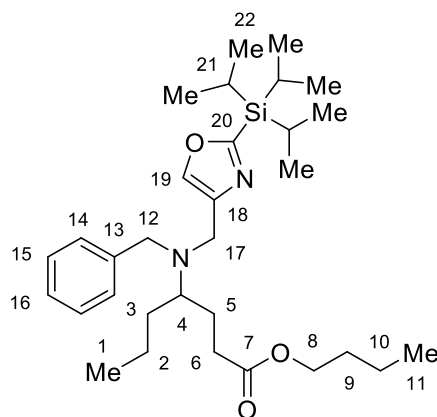
Prepared according to general procedure B using methyl 3-((benzylamino)methyl)benzoate **671a** (51 mg, 0.2 mmol), butyraldehyde (20  $\mu$ L, 0.22 mmol) and *n*-butyl acrylate (32  $\mu$ L, 0.22 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (72 mg, 81%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.46; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2956, 2932, 2872, 1722, 1603, 1494, 1452, 1433, 1359, 1282, 1198, 1173, 1105, 1079, 1027. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.98 (1 H, app s, H<sub>19</sub>), 7.89 (1 H, dt, *J* = 1.3, 7.7 Hz, H<sub>23</sub>), 7.56 (1 H, app d, *J* = 7.9 Hz, H<sub>25</sub>), 7.37 (1 H, t, *J* = 7.8 Hz, H<sub>24</sub>), 7.23 – 7.26 (4 H, m, H<sub>14</sub> and H<sub>15</sub>), 7.21 (1 H, tt, *J* = 1.8, 6.2 Hz, H<sub>16</sub>), 3.98 (2 H, dt, *J* = 3.6, 6.8 Hz, H<sub>8</sub>), 3.92 (3 H, s, H<sub>22</sub>), 3.69 (1 H, d, *J* = 13.9 Hz, H<sub>17a</sub>), 3.65 (1 H, d, *J* = 13.9 Hz, H<sub>12a</sub>), 3.53 (1 H, d, *J* = 13.6 Hz, H<sub>17b</sub>), 3.48 (1 H, d, *J* = 13.6 Hz, H<sub>12b</sub>), 2.50 – 2.41 (2 H, m, H<sub>4</sub> and H<sub>6a</sub>), 2.25 (1 H, ddd, *J* = 6.8, 9.1, 15.9 Hz, H<sub>6b</sub>), 1.87 – 1.77 (1 H, m, H<sub>5a</sub>), 1.71 – 1.61 (2 H, m, H<sub>3a</sub> and H<sub>5b</sub>), 1.59 – 1.52 (2 H, m, H<sub>9</sub>), 1.39 – 1.29 (4H, m, H<sub>2</sub> and H<sub>10</sub>), 1.26 – 1.16 (1 H, m, H<sub>3b</sub>), 0.92 (3 H, t, *J* = 7.4 Hz, H<sub>11</sub>), 0.86 (3 H, t, *J* = 7.4 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 174.1 (C<sub>21</sub>), 167.3 (C<sub>7</sub>), 141.0 (C<sub>18</sub>), 140.2 (C<sub>13</sub>), 133.6 (C<sub>25</sub>), 130.1 (C<sub>19</sub>), 130.1 (C<sub>20</sub>), 129.0 (C<sub>14</sub>), 128.4 (C<sub>24</sub>), 128.3 (C<sub>15</sub>), 128.2 (C<sub>23</sub>), 127.0 (C<sub>16</sub>), 64.3 (C<sub>8</sub>), 56.9 (C<sub>4</sub>), 53.5 (C<sub>12</sub>), 53.1 (C<sub>17</sub>), 52.2 (C<sub>22</sub>), 31.9 (C<sub>6</sub>), 31.1 (C<sub>3</sub>), 30.8 (C<sub>9</sub>), 25.6 (C<sub>5</sub>), 20.5 (C<sub>2</sub>), 19.3 (C<sub>10</sub>), 14.4 (C<sub>1</sub>), 13.9 (C<sub>11</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 440.2791, C<sub>27</sub>H<sub>38</sub>NO<sub>4</sub> requires 440.2795.

butyl 4-(benzyl(4-fluoro-3-methoxybenzyl)amino)heptanoate **672b**

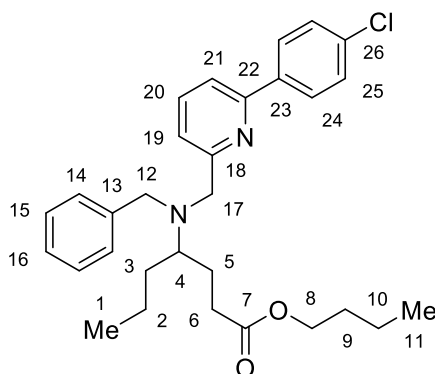
Prepared according to general procedure B using *N*-benzyl-1-(4-fluoro-3-methoxyphenyl)-methanamine **671b** (49 mg, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and *n*-butyl acrylate (58  $\mu$ L, 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (71 mg, 83%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.53; IR  $\nu_{\text{max}}$ /cm<sup>-1</sup> (film): 2956, 2933, 2872, 1730, 1610, 1514, 1453, 1417, 1372, 1269, 1212, 1171, 1150, 1117, 1071, 1033. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.35 – 7.23 (5 H, m, H<sub>14</sub>, H<sub>15</sub> and H<sub>16</sub>), 7.01 – 6.96 (2 H, m, H<sub>19</sub> and H<sub>23</sub>), 6.85 – 6.81 (1 H, m, H<sub>24</sub>), 4.01 (2 H, dt, *J* = 4.0, 6.4, H<sub>8</sub>), 3.89 (3 H, s, H<sub>21</sub>), 3.67 (1 H, d, *J* = 13.4 Hz, H<sub>12a</sub>), 3.61 (1 H, d, *J* = 13.8 Hz, H<sub>17a</sub>), 3.49 (1 H, d, *J* = 13.4 Hz, H<sub>12b</sub>), 3.45 (1 H, d, *J* = 13.8 Hz, H<sub>17b</sub>), 2.51 – 2.43 (2 H, m, H<sub>4</sub> and H<sub>6a</sub>), 2.29 (1 H, ddd, *J* = 7.1, 8.9, 15.5 Hz, H<sub>6b</sub>), 1.88 – 1.78 (1 H, m, H<sub>5a</sub>), 1.73 – 1.63 (2 H, m, H<sub>3a</sub> and H<sub>5b</sub>), 1.61 – 1.54 (2 H, m, H<sub>9</sub>), 1.37 (4 H, m, H<sub>2</sub> and H<sub>10</sub>), 1.27 – 1.21 (1 H, m, H<sub>3b</sub>), 0.95 (3 H, t, *J* = 7.1 Hz, H<sub>11</sub>), 0.89 (3 H, t, *J* = 7.3 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 174.1 (C<sub>7</sub>), 151.5 (d, *J* = 245 Hz, C<sub>22</sub>), 147.4 (d, *J* = 10.8 Hz, C<sub>20</sub>), 140.5 (C<sub>13</sub>), 136.9 (d, *J* = 3.6 Hz, C<sub>18</sub>), 129.0 (C<sub>14</sub>), 128.3 (C<sub>15</sub>), 127.0 (C<sub>16</sub>), 120.9 (d, *J* = 6.9 Hz, C<sub>24</sub>), 115.5 (d, *J* = 18.4 Hz, C<sub>23</sub>), 114.0 (d, *J* = 1.7 Hz, C<sub>19</sub>), 64.3 (C<sub>8</sub>), 56.9 (C<sub>4</sub>), 56.2 (C<sub>21</sub>), 53.4 (C<sub>12</sub>), 53.2 (C<sub>17</sub>), 31.9 (C<sub>6</sub>), 31.2 (C<sub>3</sub>), 30.8 (C<sub>9</sub>), 25.6 (C<sub>5</sub>), 20.5 (C<sub>2</sub>), 19.3 (C<sub>10</sub>), 14.4 (C<sub>1</sub>), 13.9 (C<sub>11</sub>); <sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$ : -139.3; *m/z* HRMS found [M + H]<sup>+</sup> 430.2748, C<sub>26</sub>H<sub>37</sub>FNO<sub>3</sub> requires 430.2752.

*butyl 4-(benzyl(thiophen-2-ylmethyl)amino)heptanoate* **672c**

Prepared according to general procedure B using *N*-benzyl-1-(thiophen-2-yl)methanamine (40.6 mg, 0.2 mmol), butyraldehyde (20  $\mu$ L, 0.22 mmol) and *n*-butyl acrylate (32  $\mu$ L, 0.22 mmol). The crude reaction mixture was purified by flash column chromatography (gradient elution: 100% petroleum ether to 10% ethyl acetate in petroleum ether) to afford the product as a colourless oil (62 mg, 79%).  $R_f$  (10% ethyl acetate in petroleum ether): 0.68; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2957, 2932, 2871, 1731, 1692, 1494, 1453, 1365, 1259, 1216, 1171, 1070, 1027.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.39 (2 H, d,  $J$  = 7.2 Hz,  $\text{H}_{14}$ ), 7.30 (2 H, t,  $J$  = 7.2 Hz,  $\text{H}_{15}$ ), 7.23 – 7.19 (2 H, m,  $\text{H}_{16}$  and  $\text{H}_{20}$ ), 6.90 (2 H, d,  $J$  = 3.5 Hz,  $\text{H}_{19}$  and  $\text{H}_{21}$ ), 4.00 (2 H, dt,  $J$  = 2.4 and 6.8 Hz,  $\text{H}_8$ ), 3.81 (1 H, d,  $J$  = 14.2 Hz,  $\text{H}_{17a}$ ), 3.74 – 3.70 (2 H, m,  $\text{H}_{12a}$  and  $\text{H}_{17b}$ ), 3.51 (1 H, d,  $J$  = 13.7 Hz,  $\text{H}_{12b}$ ), 2.56 – 2.49 (2 H, m,  $\text{H}_4$  and  $\text{H}_{6a}$ ), 2.30 (1 H, ddd,  $J$  = 6.6, 9.2, 15.7 Hz,  $\text{H}_{6b}$ ), 1.83 – 1.73 (1 H, m,  $\text{H}_{5a}$ ), 1.73 – 1.62 (2 H, m,  $\text{H}_{3a}$  and  $\text{H}_{5b}$ ), 1.61 – 1.54 (2 H, m,  $\text{H}_9$ ), 1.41 – 1.29 (4 H, m,  $\text{H}_2$  and  $\text{H}_{10}$ ), 1.23 – 1.14 (1 H, m,  $\text{H}_{3b}$ ), 0.93 (3 H, t,  $J$  = 7.4 Hz,  $\text{H}_{11}$ ), 0.87 (3 H, t,  $J$  = 7.1 Hz,  $\text{H}_1$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 174.3 ( $\text{C}_7$ ), 145.4 ( $\text{C}_{18}$ ), 140.1 ( $\text{C}_{13}$ ), 129.0 ( $\text{C}_{14}$ ), 128.3 ( $\text{C}_{15}$ ), 127.0 ( $\text{C}_{16}$ ), 126.4 ( $\text{C}_{21}$ ), 125.2 ( $\text{C}_{19}$ ), 124.7 ( $\text{C}_{20}$ ), 64.3 ( $\text{C}_8$ ), 56.7 ( $\text{C}_4$ ), 53.4 ( $\text{C}_{12}$ ), 48.2 ( $\text{C}_{17}$ ), 31.9 ( $\text{C}_6$ ), 31.1 ( $\text{C}_3$ ), 30.8 ( $\text{C}_9$ ), 25.7 ( $\text{C}_5$ ), 20.5 ( $\text{C}_2$ ), 19.3 ( $\text{C}_{10}$ ), 14.4 ( $\text{C}_1$ ), 13.9 ( $\text{C}_{11}$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  388.2304,  $\text{C}_{23}\text{H}_{34}\text{NO}_2\text{S}$  requires 388.2305.

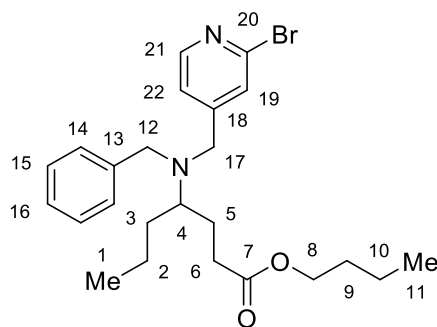
butyl 4-(benzyl((2-(triisopropylsilyl)oxazol-4-yl)methyl)amino)heptanoate **672d**

Prepared according to general procedure B using *N*-benzyl-1-(2-(triisopropylsilyl)oxazol-4-yl)methanamine **671d** (69 mg, 0.2 mmol), butyraldehyde (20  $\mu$ L, 0.22 mmol) and *n*-butyl acrylate (32  $\mu$ L, 0.22 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (76 mg, 72%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.22; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2934, 2864, 1731, 1667, 1509, 1495, 1462, 1381, 1248, 1174, 1101. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.32 (2 H, d, *J* = 7.3 Hz, H<sub>14</sub>), 7.27 (2 H, t, *J* = 7.1 Hz, H<sub>15</sub>), 7.21 (1 H, dt, *J* = 1.6, 7.2 Hz, H<sub>16</sub>), 6.94 (1 H, s, H<sub>19</sub>), 4.01 (2 H, t, *J* = 6.7 Hz, H<sub>8</sub>), 3.72 (1 H, d, *J* = 13.8 Hz, H<sub>12a</sub>), 3.69 (1 H, d, *J* = 14.7 Hz, H<sub>17a</sub>), 3.61 (1 H, d, *J* = 14.7 Hz, H<sub>17b</sub>), 3.58 (1 H, d, *J* = 13.8 Hz, H<sub>12b</sub>), 2.54 – 2.47 (2 H, m, H<sub>4</sub> and H<sub>6a</sub>), 2.22 (1 H, ddd, *J* = 6.3, 9.6, 15.8 Hz, H<sub>6b</sub>), 1.81 – 1.74 (1 H, m, H<sub>5a</sub>), 1.70 – 1.64 (1 H, m, H<sub>5b</sub>), 1.60 – 1.52 (3 H, m, H<sub>9</sub> and H<sub>3a</sub>), 1.44 – 1.28 (7 H, m, H<sub>2</sub>, H<sub>10</sub> and H<sub>21</sub>), 1.23 – 1.15 (1 H, m, H<sub>3b</sub>), 1.15 (18 H, d, *J* = 7.5 Hz, H<sub>22</sub>), 0.93 (3 H, t, *J* = 7.3 Hz, H<sub>11</sub>), 0.85 (3 H, t, *J* = 7.3 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 174.3 (C<sub>7</sub>), 168.5 (C<sub>20</sub>), 152.8 (C<sub>18</sub>), 140.1 (C<sub>13</sub>), 128.8 (C<sub>14</sub>), 128.3 (C<sub>15</sub>), 126.9 (C<sub>16</sub>), 125.0 (C<sub>19</sub>), 64.3 (C<sub>8</sub>), 58.0 (C<sub>4</sub>), 53.4 (C<sub>12</sub>), 43.9 (C<sub>17</sub>), 31.8 (C<sub>6</sub>), 31.6 (C<sub>3</sub>), 30.8 (C<sub>9</sub>), 25.9 (C<sub>5</sub>), 20.4 (C<sub>2</sub>), 19.3 (C<sub>10</sub>), 18.5 (C<sub>22</sub>), 14.4 (C<sub>1</sub>), 13.9 (C<sub>11</sub>), 11.1 (C<sub>21</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 529.3812, C<sub>31</sub>H<sub>53</sub>N<sub>2</sub>O<sub>3</sub>Si requires 529.3820.

*butyl 4-(benzyl((6-(4-chlorophenyl)pyridin-2-yl)methyl)amino)heptanoate 672e*

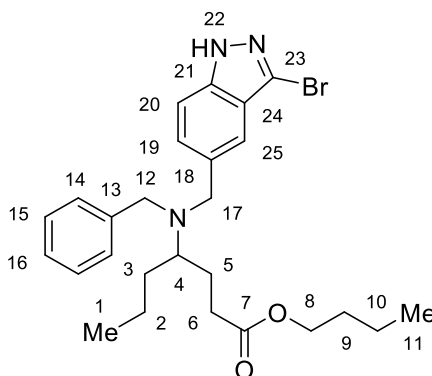
Prepared according to general procedure B using *N*-benzyl-1-(6-(4-chlorophenyl)pyridin-2-yl)methanamine **671e** (61.8 mg, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and *n*-butyl acrylate (58  $\mu$ L, 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (73 mg, 74%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.45; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2956, 2932, 2871, 1729, 1589, 1576, 1565, 1493, 1450, 1355, 1263, 1172, 1092, 1012. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.94 (2 H, dt, *J* = 1.8, 8.6 Hz, H<sub>25</sub>), 7.70 (1 H, t, *J* = 7.7 Hz, H<sub>20</sub>), 7.52 (1 H, d, *J* = 7.8 Hz, H<sub>21</sub>), 7.46 (1 H, d, *J* = 7.6 Hz, H<sub>19</sub>), 7.42 (2 H, dt, *J* = 1.8, 8.6 Hz, H<sub>24</sub>), 7.35 (2 H, d, *J* = 7.2 Hz, H<sub>14</sub>), 7.28 (2 H, t, *J* = 7.1 Hz, H<sub>15</sub>), 7.21 (1 H, t, *J* = 7.2 Hz, H<sub>16</sub>), 3.98 (2 H, dt, *J* = 2.3, 6.7 Hz, H<sub>8</sub>), 3.89 (1 H, d, *J* = 14.6 Hz, H<sub>17a</sub>), 3.76 (1 H, d, *J* = 14.6 Hz, H<sub>17b</sub>), 3.74 (1 H, d, *J* = 13.8 Hz, H<sub>12a</sub>), 3.59 (1 H, d, *J* = 13.7 Hz, H<sub>12b</sub>), 2.56 – 2.48 (2 H, m, H<sub>4</sub> and H<sub>6a</sub>), 2.30 (1 H, ddd, *J* = 6.6, 9.2, 15.7 Hz, H<sub>6b</sub>), 1.88 – 1.79 (1 H, m, H<sub>5a</sub>), 1.76 – 1.66 (2 H, m, H<sub>3a</sub> and H<sub>5b</sub>), 1.61 – 1.51 (2 H, m, H<sub>9</sub>), 1.41 – 1.29 (4 H, m, H<sub>2</sub> and H<sub>10</sub>), 1.23 – 1.14 (1 H, m, H<sub>3b</sub>), 0.91 (3 H, t, *J* = 7.3 Hz, H<sub>11</sub>), 0.88 (3 H, t, *J* = 7.3 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 174.2 (C<sub>7</sub>), 161.3 (C<sub>18</sub>), 155.3 (C<sub>22</sub>), 140.2 (C<sub>13</sub>), 138.2 (C<sub>26</sub>), 137.2 (C<sub>20</sub>), 135.0 (C<sub>23</sub>), 129.1 (C<sub>14</sub>), 129.0 (C<sub>24</sub>), 128.3 (C<sub>15</sub> or C<sub>25</sub>), 128.3 (C<sub>15</sub> or C<sub>25</sub>), 127.0 (C<sub>16</sub>), 121.4 (C<sub>19</sub>), 118.4 (C<sub>21</sub>), 64.3 (C<sub>8</sub>), 57.8 (C<sub>4</sub>), 55.6 (C<sub>17</sub>), 54.4 (C<sub>12</sub>), 32.0 (C<sub>6</sub>), 31.4 (C<sub>3</sub>), 30.8 (C<sub>9</sub>), 26.0 (C<sub>5</sub>), 20.6 (C<sub>2</sub>), 19.3 (C<sub>10</sub>), 14.4 (C<sub>1</sub>), 13.9 (C<sub>11</sub>); *m/z* HRMS found  $[\text{M} + \text{H}]^+$  493.2608 {<sup>35</sup>Cl}, C<sub>30</sub>H<sub>38</sub>ClN<sub>2</sub>O<sub>2</sub> requires 493.2616 {<sup>35</sup>Cl}.



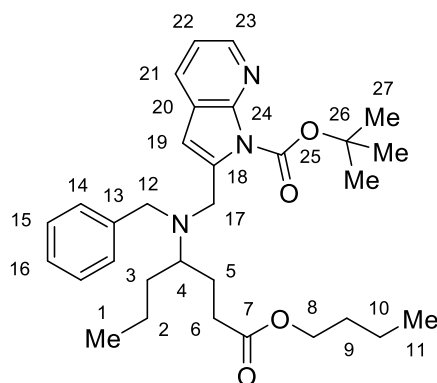
*butyl 4-(benzyl((2-bromopyridin-4-yl)methyl)amino)heptanoate 672f*

Prepared according to general procedure B using *N*-benzyl-1-(2-bromopyridin-4-yl)methanamine **671f** (55 mg, 0.2 mmol), butyraldehyde (20  $\mu$ L, 0.22 mmol) and *n*-butyl acrylate (32  $\mu$ L, 0.22 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (58 mg, 63%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.22; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2957, 2933, 2872, 1727, 1661, 1588, 1538, 1453, 1363, 1262, 1173, 1115, 1072. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.25 (1 H, d, *J* = 5.1 Hz, H<sub>21</sub>), 7.43 (1 H, s, H<sub>19</sub>), 7.33 – 7.22 (6 H, m, H<sub>14</sub>, H<sub>15</sub>, H<sub>16</sub> and H<sub>22</sub>), 4.01 (2 H, dt, *J* = 3.5, 6.9 Hz, H<sub>8</sub>), 3.61 (1 H, d, *J* = 14.9 Hz, H<sub>17a</sub>), 3.61 (1 H, d, *J* = 13.6 Hz, H<sub>12a</sub>), 3.50 (1 H, d, *J* = 13.3 Hz, H<sub>12b</sub>), 3.47 (1 H, d, *J* = 14.5 Hz, H<sub>17b</sub>), 2.47 – 2.37 (2 H, m, H<sub>4</sub> and H<sub>6a</sub>), 2.32 – 2.26 (1 H, m, H<sub>6b</sub>), 1.87 – 1.78 (1 H, m, H<sub>5a</sub>), 1.70 – 1.53 (4 H, m, H<sub>5b</sub>, H<sub>9</sub> and H<sub>3a</sub>), 1.40 – 1.30 (4 H, m, H<sub>2</sub> and H<sub>10</sub>), 1.26 – 1.19 (1 H, m, H<sub>3b</sub>), 0.92 (3 H, t, *J* = 7.3 Hz, H<sub>11</sub>), 0.87 (3 H, t, *J* = 7.3 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 173.9 (C<sub>7</sub>), 153.5 (C<sub>20</sub>), 150.0 (C<sub>21</sub>), 142.4 (C<sub>18</sub>), 139.4 (C<sub>13</sub>), 129.1 (C<sub>14</sub>), 128.5 (C<sub>15</sub>), 128.1 (C<sub>19</sub>), 127.3 (C<sub>16</sub>), 123.0 (C<sub>22</sub>), 64.5 (C<sub>8</sub>), 57.8 (C<sub>4</sub>), 53.8 (C<sub>12</sub>), 52.4 (C<sub>17</sub>), 31.8 (C<sub>6</sub>), 31.4 (C<sub>3</sub>), 30.8 (C<sub>9</sub>), 25.4 (C<sub>5</sub>), 20.4 (C<sub>2</sub>), 19.3 (C<sub>10</sub>), 14.4 (C<sub>1</sub>), 13.9 (C<sub>11</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 461.1794 {<sup>79</sup>Br}, C<sub>24</sub>H<sub>34</sub>BrN<sub>2</sub>O<sub>2</sub> requires 461.1798 {<sup>79</sup>Br}.

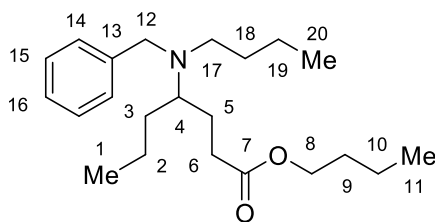
butyl 4-(benzyl((3-bromo-1*H*-indazol-5-yl)methyl)amino)heptanoate **672g**



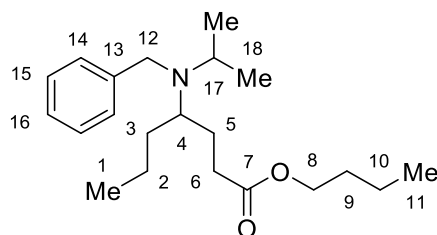
Prepared according to general procedure B using *N*-benzyl-1-(3-bromo-1*H*-indazol-5-yl)methanamine **671g** (63.2 mg, 0.2 mmol), butyraldehyde (20  $\mu$ L, 0.22 mmol) and *n*-butyl acrylate (32  $\mu$ L, 0.22 mmol). The crude reaction mixture was purified by flash column chromatography (gradient elution: 100% petroleum ether to 20% ethyl acetate in petroleum ether) to afford the product as a colourless oil (55 mg, 55%).  $R_f$  (20% ethyl acetate in petroleum ether): 0.45; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2956, 2931, 2871, 1728, 1629, 1494, 1453, 1361, 1301, 1264, 1242, 1172, 1121, 1070.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 10.85 (1 H, br s,  $\text{H}_{22}$ ), 7.49 (2 H, d,  $J = 13.4$  Hz,  $\text{H}_{19}$  and  $\text{H}_{20}$ ), 7.47 (1 H, s,  $\text{H}_{25}$ ), 7.35 – 7.28 (4 H, m,  $\text{H}_{14}$  and  $\text{H}_{15}$ ), 7.21 (1 H, tt,  $J = 1.6, 6.3$  Hz,  $\text{H}_{16}$ ), 3.96 (2 H, dt,  $J = 1.9, 7.0$  Hz,  $\text{H}_8$ ), 3.76 (1 H, d,  $J = 13.5$  Hz,  $\text{H}_{17a}$ ), 3.67 (1 H, d,  $J = 13.6$  Hz,  $\text{H}_{12a}$ ), 3.58 (1 H, d,  $J = 13.5$  Hz,  $\text{H}_{17b}$ ), 3.50 (1 H, d,  $J = 13.6$  Hz,  $\text{H}_{12b}$ ), 2.52 – 2.44 (2 H, m,  $\text{H}_4$  and  $\text{H}_{6a}$ ), 2.25 (1 H, ddd,  $J = 6.7, 8.9, 15.8$  Hz,  $\text{H}_{6b}$ ), 1.90 – 1.80 (1 H, m,  $\text{H}_{5a}$ ), 1.74 – 1.62 (3 H, m,  $\text{H}_3$  and  $\text{H}_{5b}$ ), 1.57 – 1.50 (2 H, m,  $\text{H}_9$ ), 1.39 – 1.17 (5 H, m,  $\text{H}_2$ ,  $\text{H}_{3b}$  and  $\text{H}_{10}$ ), 0.90 (3 H, t,  $J = 7.3$  Hz,  $\text{H}_{11}$ ), 0.87 (3 H, t,  $J = 7.3$  Hz,  $\text{H}_1$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 174.3 ( $\text{C}_7$ ), 140.8 ( $\text{C}_{21}$ ), 140.5 ( $\text{C}_{13}$ ), 134.4 ( $\text{C}_{18}$ ), 129.9 ( $\text{C}_{25}$ ), 129.1 ( $\text{C}_{14}$ ), 128.3 ( $\text{C}_{15}$ ), 127.0 ( $\text{C}_{16}$ ), 123.0 ( $\text{C}_{23}$ ), 122.7 ( $\text{C}_{24}$ ), 119.8 ( $\text{C}_{19}$ ), 110.3 ( $\text{C}_{20}$ ), 64.4 ( $\text{C}_8$ ), 56.7, ( $\text{C}_4$ ), 53.4 ( $\text{C}_{12}$  or  $\text{C}_{17}$ ), 53.3 ( $\text{C}_{12}$  or  $\text{C}_{17}$ ), 32.0 ( $\text{C}_6$ ), 31.1 ( $\text{C}_3$ ), 30.8 ( $\text{C}_9$ ), 25.6 ( $\text{C}_5$ ), 20.5 ( $\text{C}_2$ ), 19.3 ( $\text{C}_{10}$ ), 14.4 ( $\text{C}_1$ ), 13.9 ( $\text{C}_{11}$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  500.1900  $\{^{79}\text{Br}\}$ ,  $\text{C}_{26}\text{H}_{35}\text{BrN}_3\text{O}_2$  requires 500.1907  $\{^{79}\text{Br}\}$ .

*1-Boc-2-((benzyl(1-butoxy-1-oxoheptan-4-yl)amino)methyl)-7-azaindole 672h*

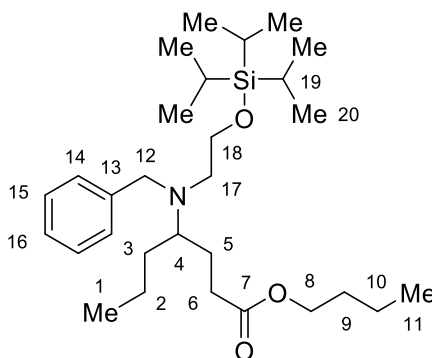
Prepared according to general procedure B using 1-Boc-2-((benzylamino)methyl)-7-azaindole **671h** (67.4 mg, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and *n*-butyl acrylate (58  $\mu$ L, 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (76 mg, 73%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.20; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2957, 2932, 2871, 1727, 1682, 1600, 1557, 1455, 1408, 1368, 1335, 1271, 1245, 1153, 1082. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.49 (1 H, dd, *J* = 1.5, 4.8 Hz, H<sub>23</sub>), 7.79 (1 H, dd, *J* = 1.7, 7.9 Hz, H<sub>21</sub>), 7.53 (1 H, s, H<sub>19</sub>), 7.34 – 7.22 (5 H, H<sub>14</sub>, H<sub>15</sub> and H<sub>16</sub>), 7.15 (1 H, dd, *J* = 4.8, 7.8 Hz, H<sub>22</sub>), 3.98 (2 H, dt, *J* = 4.1, 6.9 Hz, H<sub>8</sub>), 3.75 (1 H, d, *J* = 14.1 Hz, H<sub>17a</sub>), 3.70 (1 H, d, *J* = 13.4 Hz, H<sub>12a</sub>), 3.62 (1 H, d, *J* = 13.8 Hz, H<sub>17b</sub>), 3.52 (1 H, d, *J* = 13.4 Hz, H<sub>12b</sub>), 2.59 – 2.52 (1 H, m, H<sub>4</sub>), 2.42 (1 H, ddd, *J* = 5.9, 9.0, 14.8 Hz, H<sub>6a</sub>), 2.20 (1 H, ddd, *J* = 6.6, 8.8, 15.5 Hz, H<sub>6b</sub>), 1.93 – 1.84 (1 H, m, H<sub>5a</sub>), 1.73 – 1.65 (11 H, m, H<sub>3a</sub>, H<sub>5b</sub> and H<sub>27</sub>), 1.56 (2 H, quint, *J* = 6.9 Hz, H<sub>9</sub>), 1.39 – 1.23 (5 H, m, H<sub>2</sub>, H<sub>3b</sub> and H<sub>10</sub>), 0.93 (3 H, t, *J* = 7.3 Hz, H<sub>11</sub>), 0.87 (3 H, t, *J* = 7.3 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 174.1 (C<sub>7</sub>), 148.9 (C<sub>24</sub>), 148.0 (C<sub>25</sub>), 145.2 (C<sub>23</sub>), 140.4 (C<sub>13</sub>), 129.3 (C<sub>14</sub>), 128.5 (C<sub>21</sub>), 128.3 (C<sub>15</sub>), 127.0 (C<sub>16</sub>), 125.2 (C<sub>19</sub>), 123.2 (C<sub>18</sub>), 118.3 (C<sub>22</sub>), 116.7 (C<sub>20</sub>), 83.9 (C<sub>26</sub>), 64.3 (C<sub>8</sub>), 57.2 (C<sub>4</sub>), 53.6 (C<sub>12</sub>), 45.0 (C<sub>17</sub>), 32.0 (C<sub>6</sub>), 31.0 (C<sub>3</sub>), 30.8 (C<sub>9</sub>), 28.2 (C<sub>27</sub>), 25.4 (C<sub>5</sub>), 20.5 (C<sub>2</sub>), 19.3 (C<sub>10</sub>), 14.3 (C<sub>1</sub>), 13.8 (C<sub>11</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 522.3317, C<sub>31</sub>H<sub>44</sub>N<sub>3</sub>O<sub>4</sub> requires 522.3326.

*butyl 4-(benzyl(butyl)amino)heptanoate 672i*

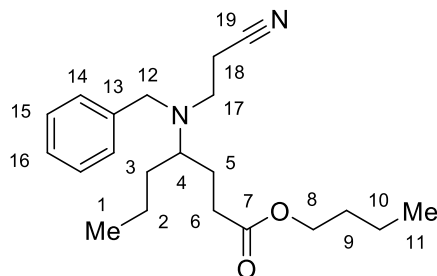
Prepared according to general procedure B using *N*-benzyl-1-butanamine (36  $\mu$ l, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and *n*-butyl acrylate (58  $\mu$ L, 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (41 mg, 58%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.75; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2956, 2929, 2871, 1732, 1494, 1454, 1377, 1247, 1174, 1065, 1027. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.32 – 7.26 (4 H, m, H<sub>14</sub> and H<sub>15</sub>), 7.20 (1 H, tt, *J* = 1.8, 6.0 Hz, H<sub>16</sub>), 4.03 (2 H, t, *J* = 6.6 Hz, H<sub>8</sub>), 3.65 (1 H, d, *J* = 14.0 Hz, H<sub>12a</sub>) 3.44 (1 H, d, *J* = 14.0 Hz, H<sub>12b</sub>), 2.50 – 2.26 (5 H, m, H<sub>4</sub>, H<sub>6</sub> and H<sub>17</sub>), 1.73 – 1.52 (5 H, m, H<sub>3a</sub>, H<sub>5</sub>, H<sub>9</sub>), 1.40 – 1.11 (9 H, m, H<sub>2</sub>, H<sub>3b</sub>, H<sub>10</sub>, H<sub>18</sub>, H<sub>19</sub>), 0.93 (3H, t, *J* = 7.4 Hz, H<sub>11</sub>), 0.88 (3 H, t, *J* = 7.4 Hz, H<sub>1</sub>), 0.83 (3 H, t, *J* = 7.3 Hz, H<sub>20</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 174.5 (C<sub>7</sub>), 141.4 (C<sub>13</sub>), 128.8 (C<sub>14</sub>), 128.1 (C<sub>15</sub>), 126.6 (C<sub>16</sub>), 64.2 (C<sub>8</sub>), 57.9 (C<sub>4</sub>), 54.2 (C<sub>12</sub>), 49.0 (C<sub>17</sub>), 32.0 (C<sub>6</sub>), 31.3 (C<sub>18</sub>), 31.2 (C<sub>3</sub>), 30.8 (C<sub>9</sub>), 26.0 (C<sub>5</sub>), 20.7 (C<sub>19</sub>), 20.6 (C<sub>2</sub>), 19.3 (C<sub>10</sub>), 14.5 (C<sub>1</sub>), 14.2 (C<sub>20</sub>), 13.9 (C<sub>11</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 348.2898, C<sub>22</sub>H<sub>38</sub>NO<sub>2</sub> requires 348.2897.

*butyl 4-(benzyl(isopropyl)amino)heptanoate 672j*

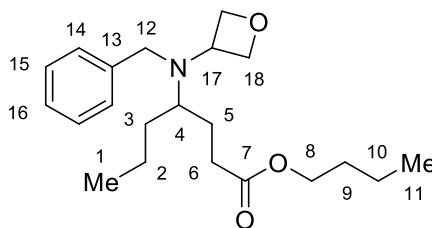
Prepared according to general procedure B using *N*-benzylpropan-2-amine (33  $\mu$ L, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and *n*-butyl acrylate (58  $\mu$ L, 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (44 mg, 65%). *R*<sub>f</sub> (10% ethyl acetate in petroleum ether): 0.60; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2958, 2932, 2871, 1732, 1688, 1493, 1453, 1380, 1360, 1247, 1163, 1131, 1113, 1069, 1026. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.32 – 7.25 (4 H, m, H<sub>14</sub> and H<sub>15</sub>), 7.19 (1 H, tt, *J* = 1.7, 6.1 Hz, H<sub>16</sub>), 4.03 (2 H, t, *J* = 6.7 Hz, H<sub>8</sub>), 3.70 (1 H, d, *J* = 14.6 Hz, H<sub>12a</sub>), 3.59 (1 H, d, *J* = 14.6 Hz, H<sub>12b</sub>), 2.95 (1 H, spt, *J* = 6.6 Hz, H<sub>17</sub>), 2.53 – 2.42 (2 H, m, H<sub>4</sub> and H<sub>6a</sub>), 2.34 – 2.27 (1 H, m, H<sub>6b</sub>), 1.68 – 1.53 (5 H, m, H<sub>3a</sub>, H<sub>5</sub> and H<sub>9</sub>), 1.41 – 1.18 (5 H, m, H<sub>2</sub>, H<sub>3b</sub> and H<sub>10</sub>), 1.01 (3 H, d, *J* = 6.6 Hz, H<sub>18a</sub>), 1.00 (3 H, d, *J* = 6.6 Hz, H<sub>18b</sub>), 0.92 (3 H, t, *J* = 7.4 Hz, H<sub>11</sub>), 0.88 (3 H, t, *J* = 7.3 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 174.6 (C<sub>7</sub>), 142.3 (C<sub>13</sub>), 128.6 (C<sub>14</sub>), 128.2 (C<sub>15</sub>), 126.5 (C<sub>16</sub>), 64.2 (C<sub>8</sub>), 55.6 (C<sub>4</sub>), 49.2 (C<sub>12</sub>), 47.5 (C<sub>17</sub>), 34.6 (C<sub>3</sub>), 32.2 (C<sub>6</sub>), 30.8 (C<sub>9</sub>), 27.6 (C<sub>5</sub>), 21.9 (C<sub>2</sub>), 20.8 (C<sub>18a</sub>), 19.6 (C<sub>10</sub>), 19.3 (C<sub>18b</sub>), 14.6 (C<sub>1</sub>), 13.9 (C<sub>11</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 334.2742, C<sub>21</sub>H<sub>36</sub>NO<sub>2</sub> requires 334.2741.

*butyl 4-(benzyl(2-((triisopropylsilyl)oxy)ethyl)amino)heptanoate 672k*

Prepared according to general procedure B using *N*-benzyl-2-((triisopropylsilyl)oxy)ethan-1-amine **671k** (62 mg, 0.2 mmol), butyraldehyde (20  $\mu$ L, 0.22 mmol) and *n*-butyl acrylate (32  $\mu$ L, 0.22 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (77 mg, 78%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.73; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2956, 2865, 1734, 1462, 1381, 1248, 1174, 1096, 1066. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.32 – 7.25 (4 H, m, H<sub>14</sub> and H<sub>15</sub>), 7.20 (1 H, tt, *J* = 1.5, 6.2 Hz, H<sub>16</sub>), 4.03 (2 H, dt, *J* = 2.1, 6.9 Hz, H<sub>8</sub>), 3.71 (1 H, d, *J* = 13.9 Hz, H<sub>12a</sub>), 3.60 – 3.53 (3 H, m, H<sub>12b</sub> and H<sub>18</sub>), 2.69 – 2.43 (4 H, m, H<sub>4</sub>, H<sub>6a</sub> and H<sub>17</sub>), 2.35 – 2.27 (1 H, m, H<sub>6b</sub>), 1.71 – 1.65 (2 H, m, H<sub>5</sub>), 1.62 – 1.53 (3 H, m, H<sub>3a</sub> and H<sub>9</sub>), 1.42 – 1.28 (4 H, m, H<sub>2</sub> and H<sub>10</sub>), 1.26 – 1.16 (1 H, m, H<sub>3b</sub>), 1.02 – 1.00 (21 H, m, H<sub>19</sub> and H<sub>20</sub>), 0.93 (3 H, t, *J* = 7.3 Hz, H<sub>11</sub>), 0.89 (3 H, t, *J* = 7.4 Hz, H<sub>11</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 174.4 (C<sub>7</sub>), 141.1 (C<sub>13</sub>), 128.9 (C<sub>14</sub>), 128.2 (C<sub>15</sub>), 126.8 (C<sub>16</sub>), 64.2 (C<sub>8</sub>), 63.2 (C<sub>18</sub>), 59.7 (C<sub>4</sub>), 55.5 (C<sub>12</sub>), 52.2 (C<sub>17</sub>), 32.0 (C<sub>3</sub>), 31.9 (C<sub>6</sub>), 30.8 (C<sub>9</sub>), 26.4 (C<sub>5</sub>), 20.6 (C<sub>2</sub>), 19.3 (C<sub>10</sub>), 18.1 (C<sub>20</sub>), 14.5 (C<sub>1</sub>), 13.9 (C<sub>11</sub>), 12.1 (C<sub>19</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 492.3878, C<sub>29</sub>H<sub>54</sub>NO<sub>3</sub>Si requires 492.3867.

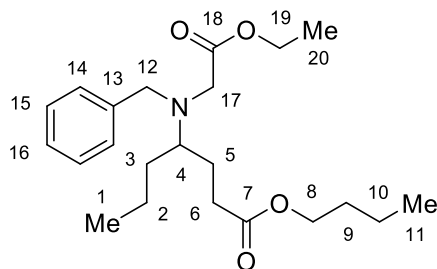
*butyl 4-(benzyl(2-cyanoethyl)amino)heptanoate* **672I**

Prepared according to general procedure B using 3-(benzylamino)propanenitrile (32  $\mu$ l, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and *n*-butyl acrylate (58  $\mu$ L, 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (39 mg, 56%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.36; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2957, 2933, 2871, 2248, 1728, 1494, 1454, 1419, 1378, 1256, 1208, 1173, 1142, 1073, 1026. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.34 – 7.29 (4 H, m, H<sub>14</sub> and H<sub>15</sub>), 7.27 – 7.22 (1 H, m, H<sub>16</sub>), 4.04 (2 H, dt, *J* = 1.0, 6.7 Hz, H<sub>8</sub>), 3.68 (1 H, d, *J* = 13.7 Hz, H<sub>12a</sub>), 3.54 (1 H, d, *J* = 13.7 Hz, H<sub>12b</sub>), 2.86 – 2.69 (2 H, m, H<sub>17</sub>), 2.56 – 2.36 (3 H, m, H<sub>4</sub> and H<sub>6</sub>), 2.28 (2 H, t, *J* = 7.0 Hz, H<sub>18</sub>), 1.76 – 1.66 (2 H, m, H<sub>5</sub>), 1.65 – 1.50 (3 H, m, H<sub>3a</sub> and H<sub>9</sub>), 1.43 – 1.33 (4 H, m, H<sub>2</sub> and H<sub>10</sub>), 1.28 – 1.19 (1 H, m, H<sub>3b</sub>), 0.93 (3 H, t, *J* = 7.4 Hz, H<sub>11</sub>), 0.91 (3 H, t, *J* = 7.3 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 174.1 (C<sub>7</sub>), 139.7 (C<sub>13</sub>), 128.9 (C<sub>14</sub>), 128.5 (C<sub>15</sub>), 127.3 (C<sub>16</sub>), 119.1 (C<sub>19</sub>), 64.4 (C<sub>8</sub>), 59.6 (C<sub>4</sub>), 54.5 (C<sub>12</sub>), 46.3 (C<sub>17</sub>), 32.0 (C<sub>3</sub>), 31.7 (C<sub>6</sub>), 30.8 (C<sub>9</sub>), 26.1 (C<sub>5</sub>), 20.5 (C<sub>2</sub>), 19.3 (C<sub>10</sub>), 18.3 (C<sub>18</sub>), 14.4 (C<sub>1</sub>), 13.9 (C<sub>11</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 345.2538, C<sub>21</sub>H<sub>33</sub>N<sub>2</sub>O<sub>2</sub> requires 345.2537.

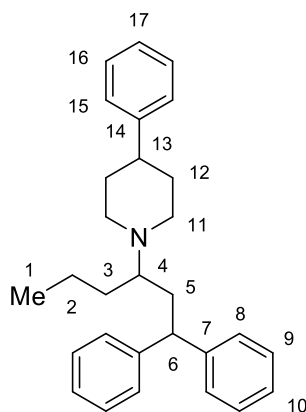
*butyl 4-(benzyl(oxetan-3-yl)amino)heptanoate* **672m**

Prepared according to general procedure B using *N*-benzyloxetan-3-amine (33 mg, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and *n*-butyl acrylate (58  $\mu$ L, 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (25 mg, 36%). *R*<sub>f</sub> (10% ethyl acetate in petroleum ether): 0.26; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2956, 2933, 2871, 1730, 1494, 1454, 1389, 1357, 1250, 1166, 1111, 1073, 1026. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.30 – 7.27 (4 H, m, H<sub>14</sub> and H<sub>15</sub>), 7.25 – 7.21 (1 H, m, H<sub>16</sub>), 4.63 (1 H, t, *J* = 6.8 Hz, H<sub>18a</sub>), 4.52 – 4.49 (3 H, m, H<sub>18b</sub>, H<sub>18c</sub> and H<sub>18d</sub>), 4.22 (1 H, quint, *J* = 7.4 Hz, H<sub>17</sub>), 4.02 (2 H, dt, *J* = 1.1, 6.8 Hz, H<sub>8</sub>), 3.90 (1 H, d, *J* = 14.0 Hz, H<sub>12a</sub>), 3.61 (1 H, d, *J* = 14.0 Hz, H<sub>12b</sub>), 2.39 – 2.33 (2 H, m, H<sub>4</sub> and H<sub>6a</sub>), 2.28 – 2.22 (1 H, m, H<sub>6b</sub>), 1.65 – 1.56 (4 H, m, H<sub>5</sub> and H<sub>9</sub>), 1.45 – 1.25 (5 H, m, H<sub>3a</sub>, H<sub>2</sub> and H<sub>10</sub>), 1.14 – 1.07 (1 H, m, H<sub>3b</sub>), 0.94 (3 H, t, *J* = 7.4 Hz, H<sub>11</sub>), 0.86 (3 H, t, *J* = 7.3 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 174.1 (C<sub>7</sub>), 140.3 (C<sub>13</sub>), 129.0 (C<sub>14</sub>), 128.3 (C<sub>15</sub>), 127.2 (C<sub>16</sub>), 77.7 (C<sub>18a</sub>), 77.0 (C<sub>18b</sub>), 64.4 (C<sub>8</sub>), 57.7 (C<sub>4</sub>), 53.9 (C<sub>17</sub>), 51.0 (C<sub>12</sub>), 32.4 (C<sub>3</sub>), 31.7 (C<sub>6</sub>), 30.8 (C<sub>9</sub>), 26.2 (C<sub>5</sub>), 20.4 (C<sub>2</sub>), 19.3 (C<sub>10</sub>), 14.3 (C<sub>1</sub>), 13.9 (C<sub>11</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 348.2535, C<sub>21</sub>H<sub>34</sub>NO<sub>3</sub> requires 348.2533.

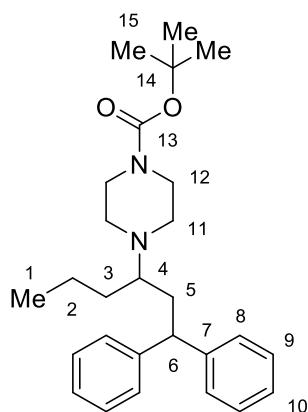


*butyl 4-(benzyl(2-ethoxy-2-oxoethyl)amino)heptanoate 672n*

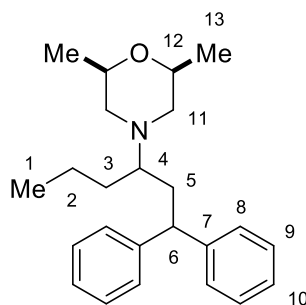
Prepared according to general procedure B using *N*-benzylglycine ethyl ester (33 mg, 0.2 mmol), butyraldehyde (20  $\mu$ L, 0.22 mmol) and *n*-butyl acrylate (32  $\mu$ L, 0.22 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (53 mg, 70%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.53; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2958, 2933, 2872, 1730, 1494, 1454, 1377, 1248, 1174, 1073, 1029. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.38 (2 H, d,  $J$  = 7.2 Hz, H<sub>14</sub>), 7.29 (2 H, t,  $J$  = 7.6 Hz, H<sub>15</sub>), 7.22 (1 H, tt,  $J$  = 1.5, 6.5 Hz, H<sub>16</sub>), 4.10 (2 H, q,  $J$  = 7.2 Hz, H<sub>19</sub>), 4.03 (2 H, t,  $J$  = 6.7 Hz, H<sub>8</sub>), 3.78 (1 H, d,  $J$  = 13.6 Hz, H<sub>12a</sub>), 3.61 (1 H, d,  $J$  = 13.6 Hz, H<sub>12b</sub>), 3.27 (1 H, d,  $J$  = 16.7 Hz, H<sub>17a</sub>), 3.19 (1 H, d,  $J$  = 16.7 Hz, H<sub>17b</sub>), 2.48 – 2.49 (2 H, m, H<sub>4</sub> and H<sub>6a</sub>), 2.41 – 2.33 (1 H, m, H<sub>6b</sub>), 1.68 (2 H, q,  $J$  = 7.45 Hz, H<sub>5</sub>), 1.62 – 1.52 (3 H, m, H<sub>3a</sub> and H<sub>9</sub>), 1.42 – 1.28 (4 H, m, H<sub>2</sub> and H<sub>10</sub>), 1.24 (3 H, t,  $J$  = 7.2 Hz, H<sub>20</sub>), 1.21 – 1.14 (1 H, m, H<sub>3b</sub>), 0.93 (3 H, t,  $J$  = 7.3 Hz, H<sub>11</sub>), 0.89 (3 H, t,  $J$  = 7.4 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 174.4 (C<sub>7</sub>), 172.4 (C<sub>18</sub>), 139.8 (C<sub>13</sub>), 129.1 (C<sub>14</sub>), 128.3 (C<sub>15</sub>), 127.1 (C<sub>16</sub>), 64.2 (C<sub>8</sub>), 60.5 (C<sub>19</sub>), 59.3 (C<sub>4</sub>), 54.9 (C<sub>12</sub>), 51.4 (C<sub>17</sub>), 32.0 (C<sub>3</sub>), 31.7 (C<sub>6</sub>), 30.8 (C<sub>9</sub>), 26.4 (C<sub>5</sub>), 20.4 (C<sub>2</sub>), 19.3 (C<sub>10</sub>), 14.4 (C<sub>1</sub>), 14.3 (C<sub>20</sub>), 13.9 (C<sub>11</sub>); *m/z* HRMS found  $[\text{M} + \text{H}]^+$  378.2639, C<sub>22</sub>H<sub>36</sub>NO<sub>4</sub> requires 378.2639.

*1-(1,1-diphenylhexan-3-yl)-4-phenylpiperidine 682a*

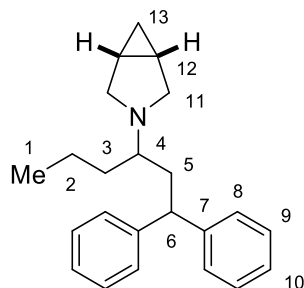
Prepared according to general procedure B using 4-phenylpiperidine (32 mg, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and 1,1-diphenylethane (72 mg, 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (40 mg, 51%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.51; IR  $\nu_{\text{max}}$ /cm<sup>-1</sup> (film): 3027, 2956, 2933, 2870, 1663, 1631, 1599, 1493, 1450, 1379, 1264, 1143, 1068, 1030. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.36 – 7.17 (15 H, m, H<sub>8</sub>, H<sub>9</sub>, H<sub>10</sub>, H<sub>15</sub>, H<sub>16</sub> and H<sub>17</sub>), 4.33 (1 H, dd, *J* = 5.7, 9.6 Hz, H<sub>6</sub>), 2.81 (1 H, d, *J* = 11.3 Hz, H<sub>11a</sub>), 2.62 – 2.45 (3 H, m, H<sub>11b</sub>, H<sub>11c</sub> and H<sub>13</sub>), 2.34 (1 H, t, *J* = 10.5 Hz, H<sub>11d</sub>), 2.29 – 2.23 (1 H, m, H<sub>4</sub>), 2.20 – 2.13 (1 H, m, H<sub>5a</sub>), 2.08 – 2.01 (1 H, m, H<sub>5b</sub>), 1.85 – 1.69 (4 H, m, H<sub>12</sub>), 1.58 – 1.53 (1 H, m, H<sub>3a</sub>), 1.38 – 1.22 (3 H, m, H<sub>2</sub> and H<sub>3b</sub>), 0.86 (3 H, t, *J* = 7.3 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 147.1 (C<sub>14</sub>), 146.0 (C<sub>7a</sub>), 145.5 (C<sub>7b</sub>), 128.5 (C<sub>8</sub> or C<sub>9</sub> or C<sub>15</sub> or C<sub>16</sub>), 128.5 (C<sub>8</sub> or C<sub>9</sub> or C<sub>15</sub> or C<sub>16</sub>), 128.4 (C<sub>8</sub> or C<sub>9</sub> or C<sub>15</sub> or C<sub>16</sub>), 128.4 (C<sub>8</sub> or C<sub>9</sub> or C<sub>15</sub> or C<sub>16</sub>), 128.1 (C<sub>8</sub> or C<sub>9</sub> or C<sub>15</sub> or C<sub>16</sub>), 127.1 (C<sub>8</sub> or C<sub>9</sub> or C<sub>15</sub> or C<sub>16</sub>), 126.1 (C<sub>17</sub>), 126.0 (C<sub>10</sub>), 61.1 (C<sub>4</sub>), 51.3 (C<sub>11a</sub>), 47.8 (C<sub>6</sub>), 47.0 (C<sub>11b</sub>), 43.5 (C<sub>13</sub>), 36.9 (C<sub>5</sub>), 34.6 (C<sub>12a</sub>), 34.3 (C<sub>12b</sub>), 31.4 (C<sub>3</sub>), 20.6 (C<sub>2</sub>), 14.4 (C<sub>1</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 398.2852, C<sub>29</sub>H<sub>36</sub>N requires 398.2842.

*1-(1,1-diphenylhexan-3-yl)-4-Boc-piperazine 682c*

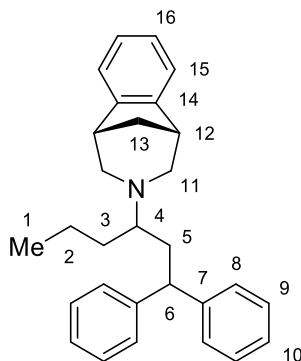
Prepared according to general procedure B using 1-Boc-piperazine (37 mg, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and 1,1-diphenylethene (72 mg, 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (32 mg, 38%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.36; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2933, 1689, 1599, 1493, 1451, 1419, 1365, 1245, 1148, 1124, 1004. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.28 – 7.22 (8 H, m, H<sub>8</sub> and H<sub>9</sub>), 7.17 – 7.13 (2 H, m, H<sub>10</sub>), 4.24 (1 H, dd, *J* = 5.5, 9.0 Hz, H<sub>6</sub>), 3.42 – 3.33 (4 H, br m, H<sub>12</sub>), 2.50 – 2.43 (2 H, br m, H<sub>11a</sub>), 2.32 – 2.25 (2 H, br m, H<sub>11b</sub>), 2.23 – 2.17 (1 H, br m, H<sub>4</sub>), 2.11 – 1.97 (2 H, m, H<sub>5</sub>), 1.45 (9 H, s, H<sub>15</sub>), 1.31 – 1.16 (4 H, m, H<sub>2</sub> and H<sub>3</sub>), 0.81 (3 H, t, *J* = 7.4 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 155.0 (C<sub>13</sub>), 145.7 (C<sub>7a</sub>), 145.1 (C<sub>7b</sub>), 128.5 (C<sub>8</sub> or C<sub>9</sub>), 128.5 (C<sub>8</sub> or C<sub>9</sub>), 128.3 (C<sub>8</sub> or C<sub>9</sub>), 128.0 (C<sub>8</sub> or C<sub>9</sub>), 126.2 (C<sub>10a</sub>), 126.1 (C<sub>10b</sub>), 79.5 (C<sub>14</sub>), 61.1 (C<sub>4</sub>), 48.0 (C<sub>11</sub>), 47.8 (C<sub>6</sub>), 44.5 (br C<sub>12</sub>), 36.6 (C<sub>5</sub>), 31.3 (C<sub>3</sub>), 28.6 (C<sub>15</sub>), 20.4 (C<sub>2</sub>), 14.3 (C<sub>1</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 423.3006, C<sub>27</sub>H<sub>39</sub>N<sub>2</sub>O<sub>2</sub> requires 423.3006.

4-(1,1-diphenylhexan-3-yl)-*cis*-2,6-dimethylmorpholine **682d**

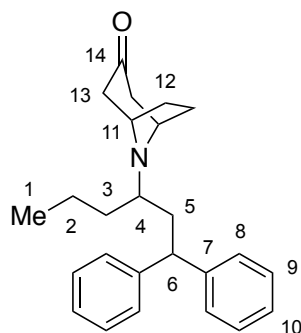
Prepared according to general procedure B using *cis*-2,6-dimethylmorpholine (25  $\mu$ L, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and 1,1-diphenylethane (72 mg, 0.4 mmol). The crude reaction mixture was filtered, the solvent removed *in vacuo* and subsequently dissolved in a solution of lithium hydroxide monohydrate (84 mg, 20 mmol) in tetrahydrofuran/water (6 mL, 5:1). The mixture was heated to a vigorous reflux for 2 hours, cooled to room temperature and diluted with saturated aqueous  $\text{NaHCO}_3$  (10 mL). The aqueous was extracted with diethyl ether (3 x 10 mL), the organics combined, and acidified with 3 M HCl (30 mL). The aqueous was washed with diethyl ether (3 x 10 mL) and then basified using  $\text{NaHCO}_3$  until pH = 10. The aqueous was extracted with dichloromethane (3 x 20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and the solvent removed *in vacuo*. The resulting oil was purified further by flash column chromatography (gradient elution: 100% petroleum ether to 10% ethyl acetate in petroleum ether with 0.5%  $\text{Et}_3\text{N}$ ) to afford the product as a colourless oil (42 mg, 60%).  $R_f$  (10% ethyl acetate in petroleum ether): 0.42; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2965, 2930, 2868, 1599, 1493, 1450, 1373, 1320, 1286, 1223, 1143, 1080.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.28 – 7.23 (8 H, m,  $\text{H}_8$  and  $\text{H}_9$ ), 7.18 – 7.13 (2 H, m,  $\text{H}_{10}$ ), 4.25 (1 H, dd,  $J = 5.7, 9.8$  Hz,  $\text{H}_6$ ), 3.70 – 3.57 (2 H, m,  $\text{H}_{12}$ ), 2.45 (1 H, d,  $J = 11.0$  Hz,  $\text{H}_{11a}$ ), 2.26 (1 H, d,  $J = 11.0$  Hz,  $\text{H}_{11b}$ ), 2.19 – 1.97 (5 H, m,  $\text{H}_5$ ,  $\text{H}_4$  and  $\text{H}_{11c}$  and  $\text{H}_{11d}$ ), 1.51 – 1.43 (1 H, m,  $\text{H}_{3a}$ ), 1.36 – 1.23 (2 H, m,  $\text{H}_2$ ), 1.19 – 1.14 (1 H, m,  $\text{H}_{3b}$ ), 1.13 (3 H, d,  $J = 6.3$  Hz,  $\text{H}_{13a}$ ), 1.13 (3 H, d,  $J = 6.3$  Hz,  $\text{H}_{13b}$ ), 0.82 (3 H, t,  $J = 7.1$  Hz,  $\text{H}_1$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 145.8 ( $\text{C}_{7a}$ ), 145.3 ( $\text{C}_{7b}$ ), 128.5 ( $\text{C}_8$  or  $\text{C}_9$ ), 128.4 ( $\text{C}_8$  or  $\text{C}_9$ ), 128.3 ( $\text{C}_8$  or  $\text{C}_9$ ), 128.0 ( $\text{C}_8$  or  $\text{C}_9$ ), 126.1 ( $\text{C}_{10a}$ ), 126.1 ( $\text{C}_{10b}$ ), 72.5 ( $\text{C}_{12a}$ ), 72.5 ( $\text{C}_{12b}$ ), 60.7 ( $\text{C}_4$ ), 56.6 ( $\text{C}_{11a}$ ), 52.6 ( $\text{C}_{11b}$ ), 47.7 ( $\text{C}_6$ ), 36.4 ( $\text{C}_5$ ), 31.0 ( $\text{C}_3$ ), 20.5 ( $\text{C}_2$ ), 19.4 ( $\text{C}_{13a}$ ), 19.3 ( $\text{C}_{13b}$ ), 14.4 ( $\text{C}_1$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  352.2631,  $\text{C}_{24}\text{H}_{34}\text{NO}$  requires 352.2635.

3-(1,1-diphenylhexan-3-yl)-3-azabicyclo[3.1.0]hexane **682e**

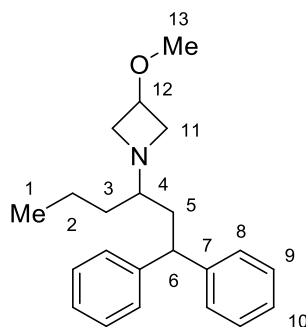
Prepared according to general procedure B using azabicyclo[3.1.0]hexane hydrochloride (24 mg, 0.2 mmol), triethylamine (28  $\mu$ L, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and 1,1-diphenylethene (72 mg, 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (16 mg, 25%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.28; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2957, 2871, 1672, 1598, 1493, 1450, 1380, 1265, 1076, 1030. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.28 – 7.20 (8 H, m, H<sub>8</sub> and H<sub>9</sub>), 7.17 – 7.14 (2 H, m, H<sub>10</sub>), 4.12 (1 H, dd, *J* = 6.8, 8.6 Hz, H<sub>6</sub>), 2.73 (1 H, d, *J* = 8.1 Hz, H<sub>11a</sub>), 2.63 (2 H, d, *J* = 1.4 Hz, H<sub>11b</sub> and H<sub>11c</sub>), 2.54 (1 H, dd, *J* = 3.5, 8.0 Hz, H<sub>11d</sub>), 2.28 (1 H, quint, *J* = 6.7 Hz, H<sub>4</sub>), 2.04 (2 H, ddd, *J* = 3.4, 5.4, 9.4 Hz, H<sub>5</sub>), 1.44 – 1.38 (1 H, m, H<sub>3a</sub>), 1.32 – 1.13 (5 H, m, H<sub>2</sub>, H<sub>3b</sub> and H<sub>12</sub>), 0.82 (3 H, t, *J* = 7.1 Hz, H<sub>1</sub>), 0.74 (1 H, q, *J* = 3.8 Hz, H<sub>13a</sub>), 0.35 (1 H, dt, *J* = 3.9, 7.6 Hz, H<sub>13b</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 145.9 (C<sub>7a</sub>), 145.3 (C<sub>7b</sub>), 128.4 (C<sub>8</sub> or C<sub>9</sub>), 128.4 (C<sub>8</sub> or C<sub>9</sub>), 128.3 (C<sub>8</sub> or C<sub>9</sub>), 127.0 (C<sub>8</sub> or C<sub>9</sub>), 126.0 (C<sub>10a</sub>), 126.0 (C<sub>10b</sub>), 55.0 (C<sub>4</sub>), 50.6 (C<sub>11a</sub>), 47.7 (C<sub>6</sub>), 46.7 (C<sub>11b</sub>), 38.1 (C<sub>5</sub>), 32.0 (C<sub>3</sub>), 20.0 (C<sub>2</sub>), 15.3 (C<sub>12a</sub>), 15.1 (C<sub>12b</sub>), 14.5 (C<sub>1</sub>), 7.1 (C<sub>13</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 320.2375, C<sub>23</sub>H<sub>30</sub>N requires 320.2373.

3-(1,1-diphenylhexan-3-yl)-2,3,4,5-tetrahydro-1*H*-1,5-methanobenzo[*d*]azepine **682f**

Prepared according to general procedure B using 2,3,4,5-tetrahydro-1*H*-1,5-methanobenzo[*d*]azepine hydrochloride (39 mg, 0.2 mmol), triethylamine (28  $\mu$ L, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and 1,1-diphenylethene (72 mg, 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) and the subsequent oil dissolved in 10% aqueous HCl (10 mL) and washed with diethyl ether (3 x 10 mL). The aqueous was adjusted to pH = 10 using solid NaOH with cooling and extracted with dichloromethane (3 x 10 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent removed *in vacuo* to afford the product as a white gum (30 mg, 38%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.84; IR  $\nu_{\text{max}}$ /cm<sup>-1</sup> (film): 2932, 2869, 1716, 1661, 1599, 1493, 1450, 1375, 1265, 1151, 1065, 1029. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.30 – 7.18 (7 H, m, H<sub>8</sub> or H<sub>9</sub> or H<sub>10</sub> or H<sub>15</sub> or H<sub>16</sub>), 7.13 – 7.03 (5 H, m, H<sub>8</sub> or H<sub>9</sub> or H<sub>10</sub> or H<sub>15</sub> or H<sub>16</sub>), 6.70 (2 H, d, *J* = 7.20, H<sub>8</sub>), 3.26 (1 H, dd, *J* = 2.6, 11.4 Hz, H<sub>6</sub>), 3.10 – 3.07 (2 H, m, H<sub>12</sub>), 2.89 (1 H, d, *J* = 9.8 Hz, H<sub>11a</sub>), 2.69 (1 H, dd, *J* = 2.9, 10.0 Hz, H<sub>11b</sub>), 2.59 (1 H, d, *J* = 9.9 Hz, H<sub>11c</sub>), 2.32 – 2.27 (2 H, m, H<sub>11d</sub> and H<sub>13a</sub>), 1.96 – 1.83 (2 H, m, H<sub>4</sub> and H<sub>5a</sub>), 1.73 (1 H, dt, *J* = 3.5, 10.5 Hz, H<sub>5b</sub>), 1.67 (1 H, d, *J* = 10.2 Hz, H<sub>13b</sub>), 1.53 – 1.45 (1 H, m, H<sub>3a</sub>), 1.25 – 1.00 (3 H, m, H<sub>2</sub> and H<sub>3b</sub>), 0.78 (3 H, t, *J* = 7.1 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 147.1 (C<sub>14a</sub>), 147.1 (C<sub>14b</sub>), 146.7 (C<sub>7a</sub>), 144.8 (C<sub>7b</sub>), 128.4 (C<sub>8</sub> or C<sub>9</sub>), 128.2 (C<sub>8</sub> or C<sub>9</sub>), 127.9 (C<sub>8</sub> or C<sub>9</sub>), 127.8 (C<sub>8</sub> or C<sub>9</sub>), 126.6 (C<sub>15</sub> or C<sub>16</sub>), 126.4 (C<sub>15</sub> or C<sub>16</sub>), 125.7 (C<sub>10</sub>), 125.7 (C<sub>10</sub>), 121.9 (C<sub>15</sub> or C<sub>16</sub>), 121.7 (C<sub>15</sub> or C<sub>16</sub>), 59.1 (C<sub>4</sub>), 55.5 (C<sub>11a</sub>), 47.7 (C<sub>11b</sub>), 46.2 (C<sub>6</sub>), 44.2 (C<sub>13</sub>), 41.8 (C<sub>12a</sub>), 41.2 (C<sub>12b</sub>), 37.2 (C<sub>5</sub>), 31.6 (C<sub>3</sub>), 20.7 (C<sub>2</sub>), 14.4 (C<sub>1</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 396.2686, C<sub>29</sub>H<sub>34</sub>N requires 396.2694

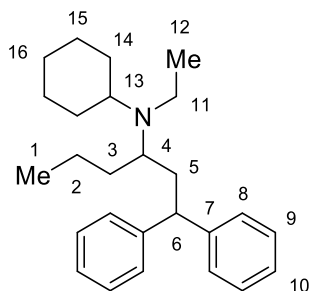
8-(1,1-diphenylhexan-3-yl)-8-azabicyclo[3.2.1]octan-3-one **682g**

Prepared according to general procedure B using nortropinone hydrochloride (49 mg, 0.2 mmol), triethylamine (28  $\mu$ L, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and 1,1-diphenylethene (72 mg, 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a colourless oil (24 mg, 34%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.12; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2955, 2871, 1710, 1598, 1493, 1450, 1412, 1348, 1265, 1193, 1135, 1075, 1030. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.30 – 7.26 (8 H, m, H<sub>8</sub> and H<sub>9</sub>), 7.20 – 7.16 (2 H, m, H<sub>10</sub>), 4.10 (1 H, dd, *J* = 5.8, 10.0 Hz, H<sub>6</sub>), 3.71 (1 H, br s, H<sub>11a</sub>), 3.58 (1 H, br s, H<sub>11b</sub>), 2.61 – 2.57 (1 H, m, H<sub>4</sub>), 2.49 (1 H, dd, *J* = 3.8, 15.5 Hz, H<sub>13a</sub>), 2.35 – 2.28 (2 H, m, H<sub>5a</sub> and H<sub>13b</sub>), 2.26 – 2.20 (1 H, m, H<sub>5b</sub>), 2.10 (1 H, d, *J* = 15.5 Hz, H<sub>13c</sub>), 2.04 (1 H, d, *J* = 15.5 Hz, H<sub>13d</sub>), 1.91 – 1.82 (2 H, br m, H<sub>12a</sub>), 1.62 – 1.53 (3 H, m, H<sub>3a</sub> and H<sub>12b</sub>), 1.52 – 1.35 (3 H, m, H<sub>2</sub> and H<sub>3b</sub>), 0.91 (3 H, t, *J* = 7.4 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 210.9 (C<sub>14</sub>), 145.4 (C<sub>7a</sub>), 144.7 (C<sub>7b</sub>), 128.8 (C<sub>8</sub> or C<sub>9</sub>), 128.6 (C<sub>8</sub> or C<sub>9</sub>), 128.1 (C<sub>8</sub> or C<sub>9</sub>), 127.8 (C<sub>8</sub> or C<sub>9</sub>), 126.6 (C<sub>10a</sub>), 126.3 (C<sub>10b</sub>), 56.5 (C<sub>11a</sub>), 55.2 (C<sub>11b</sub>), 53.9 (C<sub>4</sub>), 48.5 (C<sub>6</sub>), 47.2 (C<sub>13a</sub>), 47.0 (C<sub>13b</sub>), 38.3 (C<sub>5</sub>), 33.9 (C<sub>3</sub>), 29.4 (C<sub>12a</sub>), 29.3 (C<sub>12b</sub>), 17.7 (C<sub>2</sub>), 14.8 (C<sub>1</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 362.2483, C<sub>25</sub>H<sub>32</sub>NO requires 362.2478.

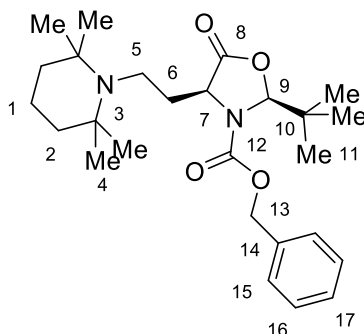
*1-(1,1-diphenylhexan-3-yl)-3-methoxyazetidine 682h*

Prepared according to general procedure B using 3-methoxyazetidine hydrochloride (25 mg, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol), triethylamine (28  $\mu$ L, 0.2 mmol) and 1,1-diphenylethene (72 mg, 0.4 mmol). The crude reaction mixture was filtered, the solvent removed *in vacuo* and subsequently dissolved in a solution of lithium hydroxide monohydrate (84 mg, 20 mmol) in tetrahydrofuran/water (6 mL, 5:1). The mixture was heated to a vigorous reflux for 2 hours, cooled to room temperature and diluted with saturated aqueous  $\text{NaHCO}_3$  (10 mL). The aqueous was extracted with diethyl ether (3 x 10 mL), the organics combined, and acidified with 3 M  $\text{HCl}$  (30 mL). The aqueous was washed with diethyl ether (3 x 10 mL) and then basified using  $\text{NaHCO}_3$  until pH = 10. The aqueous was extracted with dichloromethane (3 x 20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and the solvent removed *in vacuo*. The resulting oil was purified further by flash column chromatography (gradient elution: 10% ethyl acetate in petroleum ether to 30% ethyl acetate in petroleum ether with 0.5%  $\text{Et}_3\text{N}$ ) to afford the product as a colourless oil (52 mg, 81%).  $R_f$  (50% ethyl acetate in petroleum ether): 0.14; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2929, 2871, 2824, 1721, 1598, 1494, 1450, 1366, 1221, 1188, 1124.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.34 – 7.16 (10 H, m,  $\text{H}_8$ ,  $\text{H}_9$  and  $\text{H}_{10}$ ), 4.03 – 3.96 (2 H, m,  $\text{H}_4$  and  $\text{H}_{12}$ ), 3.62 (1 H, t,  $J = 5.5$  Hz,  $\text{H}_{11a}$ ), 3.50 (1 H, t,  $J = 5.5$  Hz,  $\text{H}_{11b}$ ), 3.24 (3 H, s,  $\text{H}_{13}$ ), 2.81 (1 H, t,  $J = 6.4$  Hz,  $\text{H}_{11c}$ ), 2.76 (1 H, t,  $J = 6.7$  Hz,  $\text{H}_{11d}$ ), 2.19 – 2.08 (2 H, m,  $\text{H}_4$  and  $\text{H}_{5a}$ ), 2.04 – 1.98 (1 H, m,  $\text{H}_{5b}$ ), 1.44 – 1.28 (4 H, m,  $\text{H}_2$  and  $\text{H}_3$ ), 0.87 (3 H, t,  $J = 6.4$  Hz,  $\text{H}_1$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 145.6 ( $\text{C}_{7a}$ ), 144.6 ( $\text{C}_{7b}$ ), 128.7 ( $\text{C}_8$  or  $\text{C}_9$ ), 128.6 ( $\text{C}_8$  or  $\text{C}_9$ ), 128.2 ( $\text{C}_8$  or  $\text{C}_9$ ), 127.8 ( $\text{C}_8$  or  $\text{C}_9$ ), 126.4 ( $\text{C}_{10a}$ ), 126.2 ( $\text{C}_{10b}$ ), 69.4 ( $\text{C}_{12}$ ), 64.4 ( $\text{C}_4$ ), 59.8 ( $\text{C}_{11a}$ ), 59.4 ( $\text{C}_{11b}$ ), 56.1 ( $\text{C}_{13}$ ), 48.2 ( $\text{C}_6$ ), 36.8 ( $\text{C}_5$ ), 32.5 ( $\text{C}_3$ ), 17.7 ( $\text{C}_2$ ), 14.8 ( $\text{C}_1$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  324.2320,  $\text{C}_{22}\text{H}_{30}\text{NO}$  requires 324.2322.



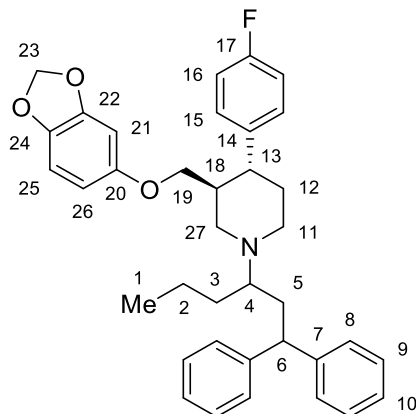
*N*-(1,1-diphenylhexan-3-yl)-*N*-ethylcyclohexanamine **682i**

Prepared according to general procedure B using *N*-ethylcyclohexylamine (30  $\mu$ L, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and 1,1-diphenylethene (72 mg, 0.4 mmol). The crude reaction mixture was filtered, the solvent removed *in vacuo* and subsequently dissolved in a solution of lithium hydroxide monohydrate (84 mg, 20 mmol) in tetrahydrofuran/water (6 mL, 5:1). The mixture was heated to a vigorous reflux for 2 hours, cooled to room temperature and diluted with saturated aqueous  $\text{NaHCO}_3$  (10 mL). The aqueous was extracted with diethyl ether (3 x 10 mL), the organics combined, and acidified with 3 M  $\text{HCl}$  (30 mL). The aqueous was washed with diethyl ether (3 x 10 mL) and then basified using  $\text{NaHCO}_3$  until  $\text{pH} = 10$ . The aqueous was extracted with dichloromethane (3 x 20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and the solvent removed *in vacuo*. The resulting oil was purified further by flash column chromatography (gradient elution: 100% petroleum ether to 5% ethyl acetate in petroleum ether with 0.5%  $\text{Et}_3\text{N}$ ) to afford the product as a colourless oil (50 mg, 69%).  $R_f$  (10% ethyl acetate in petroleum ether): 0.30; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2926, 2853, 1729, 1599, 1493, 1448, 1377, 1262, 1177, 1131, 1072, 1030.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.29 – 7.11 (10 H, m,  $\text{H}_8$ ,  $\text{H}_9$  and  $\text{H}_{10}$ ), 4.24 (1 H, dd,  $J = 5.7, 9.1$  Hz,  $\text{H}_6$ ), 2.60 – 2.41 (4 H, m,  $\text{H}_4$ ,  $\text{H}_{11}$  and  $\text{H}_{13}$ ), 2.12 (1 H, ddd,  $J = 4.9, 9.4, 14.0$  Hz,  $\text{H}_{5a}$ ), 1.95 (1 H, ddd,  $J = 6.0, 8.4, 14.0$  Hz,  $\text{H}_{5b}$ ), 1.69 – 1.52 (5 H, m,  $\text{H}_{3a}$ ,  $\text{H}_{14a}$ ,  $\text{H}_{15a}$ ,  $\text{H}_{16}$ ), 1.45 – 1.03 (9 H, m,  $\text{H}_2$ ,  $\text{H}_{3b}$ ,  $\text{H}_{14b}$ ,  $\text{H}_{14c}$ ,  $\text{H}_{14d}$ ,  $\text{H}_{15b}$ ,  $\text{H}_{15c}$  and  $\text{H}_{15d}$ ), 0.87 – 0.83 (6 H, m,  $\text{H}_1$  and  $\text{H}_{12}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 146.8 ( $\text{C}_{7a}$ ), 144.8 ( $\text{C}_{7b}$ ), 128.7 ( $\text{C}_8$  or  $\text{C}_9$ ), 128.5 ( $\text{C}_8$  or  $\text{C}_9$ ), 128.4 ( $\text{C}_8$  or  $\text{C}_9$ ), 128.0 ( $\text{C}_8$  or  $\text{C}_9$ ), 126.0 ( $\text{C}_{10a}$ ), 125.9 ( $\text{C}_{10b}$ ), 57.5 ( $\text{C}_{13}$ ), 55.4 ( $\text{C}_4$ ), 48.2 ( $\text{C}_6$ ), 39.2 ( $\text{C}_5$ ), 38.9 ( $\text{C}_{11}$ ), 35.0 ( $\text{C}_{14a}$ ), 33.1 ( $\text{C}_{14b}$ ), 31.8 ( $\text{C}_3$ ), 26.8 ( $\text{C}_{15a}$  or  $\text{C}_{15b}$  or  $\text{C}_{16}$ ), 26.8 ( $\text{C}_{15a}$  or  $\text{C}_{15b}$  or  $\text{C}_{16}$ ), 26.4 ( $\text{C}_{15a}$  or  $\text{C}_{15b}$  or  $\text{C}_{16}$ ), 20.7 ( $\text{C}_2$ ), 16.8 ( $\text{C}_{12}$ ), 14.6 ( $\text{C}_1$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  364.2997,  $\text{C}_{26}\text{H}_{38}\text{N}$  requires 364.2999.

*(2S,4S)*-2-(*tert*-butyl)-3-Cbz-4-(2-(2,2,6,6-tetramethylpiperidin-1-yl)ethyl)oxazolidin-5-one **682I**

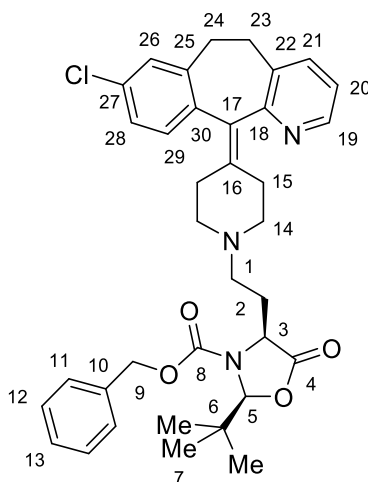
Prepared according to general procedure C using 2,2,6,6-tetramethylpiperidine (34  $\mu$ L, 0.2 mmol), paraformaldehyde (30 mg, 1.0 mmol) and (*S*)-2-(*tert*-butyl)-3-Cbz-4-methyleneoxazolidin-5-one **668** (85 mg, 0.3 mmol). The crude reaction mixture was purified twice by flash column chromatography (gradient elution: 10% ethyl acetate in petroleum ether to 20% ethyl acetate in petroleum ether with 0.5% Et<sub>3</sub>N) to afford the product as a colourless viscous oil (54 mg, 61%, d.r. >20:1). *R*<sub>f</sub> (25% ethyl acetate in petroleum ether): 0.33; IR  $\nu_{\text{max}}$ /cm<sup>-1</sup> (film): 2963, 2928, 1790, 1717, 1481, 1466, 1391, 1332, 1289, 1261, 1228, 1198, 1175. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.38 – 7.32 (5 H, m, H<sub>15</sub>, H<sub>16</sub> and H<sub>17</sub>), 5.56 (1 H, s, H<sub>9</sub>), 5.16 (2 H, d, *J* = 2.1 Hz, H<sub>13</sub>), 4.14 (1 H, dd, *J* = 5.8, 8.0 Hz, H<sub>7</sub>), 2.82 – 2.74 (1 H, m, H<sub>5a</sub>), 2.57 – 2.49 (1 H, m, H<sub>5b</sub>), 2.05 – 1.87 (2 H, m, H<sub>6</sub>), 1.53 – 1.47 (2 H, m, H<sub>1</sub>), 1.35 (4 H, app t, *J* = 5.7 Hz, H<sub>2</sub>), 0.96 (12 H, s, H<sub>4</sub>), 0.94 (9 H, s, H<sub>11</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 173.1 (C<sub>8</sub>), 156.0 (C<sub>12</sub>), 135.3 (C<sub>14</sub>), 128.9 (C<sub>15</sub>), 128.8 (C<sub>17</sub>), 128.7 (C<sub>16</sub>), 96.6 (C<sub>9</sub>), 68.5 (C<sub>13</sub>), 55.9 (C<sub>7</sub>), 54.7 (C<sub>3</sub>), 42.3 (C<sub>5</sub>), 41.2 (C<sub>2</sub>), 39.1 (C<sub>6</sub>), 37.2 (C<sub>10</sub>), 25.0 (C<sub>4</sub> and C<sub>11</sub>), 17.8 (C<sub>1</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 445.3053, C<sub>26</sub>H<sub>41</sub>N<sub>2</sub>O<sub>4</sub> requires 445.3061.

*(3S,4R)*-3-((benzo[d][1,3]dioxol-5-yloxy)methyl)-1-(1,1-diphenylhexan-3-yl)-4-(4-fluorophenyl)piperidine **685a**



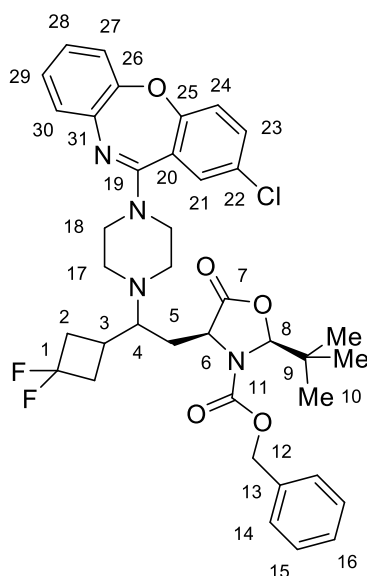
Prepared according to general procedure B using paroxetine hydrochloride (63 mg, 0.2 mmol), triethylamine (28  $\mu$ L, 0.2 mmol), butyraldehyde (36  $\mu$ L, 0.4 mmol) and 1,1-diphenylethene (72 mg, 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (0.5% Et<sub>3</sub>N in dichloromethane) to afford the product as a gum (49 mg, 44%, d.r. 1:1).  $R_f$  (10% ethyl acetate in petroleum ether): 0.33; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2918, 1633, 1602, 1508, 1502, 1487, 1466, 1450, 1381, 1268, 1222, 1182, 1158, 1135, 1090, 1038.  $^1\text{H}$  NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.33 – 7.26 (8 H, m, H<sub>8</sub> and H<sub>9</sub>), 7.22 – 7.17 (4 H, m, H<sub>10</sub> and H<sub>15</sub>), 7.00 (2 H, t,  $J$  = 8.5 Hz, H<sub>16</sub>), 6.64 (1 H, dd,  $J$  = 5.2, 8.6 Hz, H<sub>25</sub>), 6.36 (1 H, app s, H<sub>21</sub>), 6.15 (1 H, dd,  $J$  = 2.2, 8.5 Hz, H<sub>26</sub>), 5.89 (2 H, s, H<sub>23</sub>), 4.32 (1 H, dd,  $J$  = 5.7, 9.2 Hz, H<sub>6</sub>), 3.57 (1 H, dd,  $J$  = 2.6, 9.5 Hz, H<sub>19a</sub>), 3.45 (1 H, app t,  $J$  = 7.9 Hz, H<sub>19b</sub>), [3.07 (dd,  $J$  = 2.3, 10.7 Hz), 2.46 – 2.01 (m), total 1 H, H<sub>27a</sub>], [2.87 (d,  $J$  = 9.9 Hz), 2.46 – 2.01 (m), total 1 H, H<sub>27b</sub>], [2.78 (d,  $J$  = 11.3 Hz), 2.46 – 2.01 (m), total 1 H, H<sub>11a</sub>], 2.59 – 2.49 (1 H, m, H<sub>11b</sub>), 2.45 – 2.03 (5 H, m, H<sub>4</sub>, H<sub>5</sub>, H<sub>13</sub> and H<sub>18</sub>), 1.80 – 1.70 (2 H, m, H<sub>12</sub>), 1.62 – 1.52 (1 H, m, H<sub>3a</sub>), 1.37 – 1.18 (3 H, m, H<sub>2</sub> and H<sub>3a</sub>), 0.89 – 0.84 (3 H, m, H<sub>1</sub>);  $^{13}\text{C}$  NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 161.6 (d,  $J$  = 245.0 Hz, C<sub>17</sub>), [154.6, 154.6, C<sub>20</sub>], 148.3 (C<sub>22</sub>), [146.0, 145.9, 145.4, 145.3, C<sub>7</sub>], 141.6 (C<sub>24</sub>), 140.3 (app t,  $J$  = 3.0 Hz, C<sub>14</sub>), 129.0 (d,  $J$  = 7.9 Hz, C<sub>15</sub>), [128.5, 128.4, 128.4, 128.4] (C<sub>8</sub>), 128.1 (C<sub>9</sub>), [126.1, 126.0, C<sub>10</sub>], 115.4 (d,  $J$  = 21.0 Hz, C<sub>16</sub>), 108.0 (C<sub>25</sub>), [105.8, 105.7, C<sub>26</sub>], 101.2 (C<sub>23</sub>), 98.1 (C<sub>21</sub>), [70.1, 70.0, C<sub>19</sub>], 61.4 (C<sub>4</sub>), 54.8 (C<sub>27a</sub>), 51.2 (C<sub>11a</sub>), 50.5 (C<sub>27b</sub>), [48.0, 47.9, C<sub>6</sub>], 46.9 (C<sub>11b</sub>), [45.2, 45.1, C<sub>13</sub>], [43.0, 42.8, C<sub>18</sub>], [37.0, 36.8, C<sub>5</sub>], [35.5, 35.4, C<sub>12</sub>], [31.4, 31.3, C<sub>3</sub>], [20.6, 20.6, C<sub>2</sub>], 14.4 (C<sub>1</sub>);  $^{19}\text{F}$  { $^1\text{H}$ } NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$ : -117.8, -117.8;  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  566.3052, C<sub>37</sub>H<sub>41</sub>FNO<sub>3</sub> requires 566.3065.

(2*S*,4*S*)-2-(*tert*-butyl)-3-Cbz-(4-(8-chloro-5,6-dihydro-1*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidin-1-yl)ethyl)oxazolidin-5-one **685b**

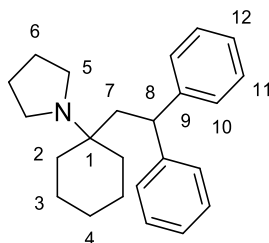


Prepared according to general procedure C using desloratidine (62 mg, 0.2 mmol), paraformaldehyde (30 mg, 1.0 mmol) and (*S*)-2-(*tert*-butyl)-3-Cbz-4-methyleneoxazolidin-5-one **668** (62 mg, 0.22 mmol). The crude reaction mixture was purified twice by flash column chromatography (2% methanol in dichloromethane with 0.5% Et<sub>3</sub>N) and subsequently (ethyl acetate) to afford the product as an off-white solid (39 mg, 32%, d.r. >20:1) that decomposes slowly in solution. *R*<sub>f</sub> (10% methanol in dichloromethane): 0.31; m.p. 124 – 128 °C; IR  $\nu_{\text{max}}$ /cm<sup>-1</sup> (film): 2962, 1789, 1716, 1588, 1562, 1479, 1438, 1393, 1297, 1262, 1228, 1196, 1116, 1088, 1040, 1014. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.41 (1 H, t, *J* = 4.3 Hz, H<sub>19</sub>), 7.44 (1 H, d, *J* = 7.5 Hz, H<sub>21</sub>), 7.33 – 7.26 (5 H, m, H<sub>11</sub>, H<sub>12</sub> and H<sub>13</sub>), 7.15 – 7.07 (4 H, m, H<sub>20</sub>, H<sub>26</sub>, H<sub>28</sub> and H<sub>29</sub>), 5.55 (1 H, s, H<sub>5</sub>), 5.24 (2 H, t, *J* = 6.1 Hz, H<sub>9</sub>), 4.51 – 4.46 (1 H, m, H<sub>3</sub>), 3.44 – 3.32 (2 H, m, H<sub>23a</sub> and H<sub>24a</sub>), 2.87 – 2.20 (11 H, m, H<sub>1</sub>, H<sub>14</sub>, H<sub>15a</sub>, H<sub>15b</sub>, H<sub>15c</sub>, H<sub>23b</sub> and H<sub>24b</sub>), 2.12 – 1.98 (3 H, m, H<sub>2</sub> and H<sub>15d</sub>), 0.95 (9 H, s, H<sub>7</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 172.8 (C<sub>4</sub>), 157.7 (C<sub>18</sub>), 155.9 (C<sub>8</sub>), 146.8 (C<sub>19a</sub>), 146.8 (C<sub>19b</sub>), 139.6, 137.9, 137.9, 137.4 (C<sub>21</sub>), 137.4 (C<sub>21</sub>), 135.3 (C<sub>10</sub>), 133.5, 132.8, 131.0, 129.1, 129.1, 128.8, 128.8, 128.7, 128.7, 126.2, 126.1, 122.2, 96.4 (C<sub>5</sub>), 68.5 (C<sub>9</sub>), 55.1 – 55.0 (multiple C, C<sub>3</sub>), 54.6 – 54.5 (multiple C, C<sub>14</sub>), 37.2 (C<sub>6</sub>), 32.0 (C<sub>23a</sub> or C<sub>24a</sub>), 31.9 (C<sub>23a</sub> or C<sub>24a</sub>), 31.6 (C<sub>23b</sub> or C<sub>24b</sub>), 31.6 (C<sub>23b</sub> or C<sub>24b</sub>), 31.2 – 30.6 (br, C<sub>2</sub> and C<sub>15</sub>), 25.0 (C<sub>7</sub>); m/z HRMS found [M + H]<sup>+</sup> 614.2778 {<sup>35</sup>Cl}, C<sub>36</sub>H<sub>41</sub>N<sub>3</sub>O<sub>4</sub>Cl requires 614.2780 {<sup>35</sup>Cl}.

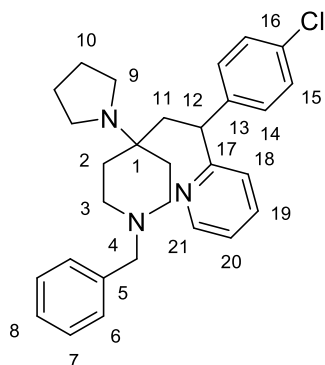
(2*S*,4*S*)-2-(*tert*-butyl)-3-Cbz-4-(2-(4-(2-chlorodibenzo[*b,f*][1,4]oxazepin-11-yl)piperazin-1-yl)-2-(3,3-difluorocyclobutyl)ethyl)oxazolidin-5-one **685c**



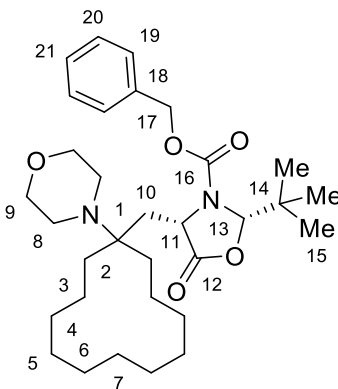
Prepared according to general procedure B using amoxapine (63 mg, 0.2 mmol), 3,3-difluorocyclobutane-1-carbaldehyde (48 mg, 0.4 mmol) and (*S*)-2-(*tert*-butyl)-3-Cbz-4-methyleneoxazolidin-5-one **668** (62 mg, 0.22 mmol). The crude reaction mixture was purified by flash column chromatography (gradient elution: 5% ethyl acetate in petroleum ether to 15% ethyl acetate in petroleum ether with 0.5% Et<sub>3</sub>N) to afford the product as a pale brown gum (78 mg, 55%, d.r. 1:1). *R<sub>f</sub>* (20% ethyl acetate in petroleum ether): 0.43; IR  $\nu_{\text{max}}$ /cm<sup>-1</sup> (film): 2961, 1788, 1716, 1600, 1587, 1557, 1470, 1454, 1397, 1367, 1345, 1295, 1240, 1197, 1170, 1112, 1040. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.42 – 6.94 (12 H, m, H<sub>14</sub>, H<sub>15</sub>, H<sub>16</sub>, H<sub>21</sub>, H<sub>23</sub>, H<sub>24</sub>, H<sub>27</sub>, H<sub>28</sub>, H<sub>29</sub> and H<sub>30</sub>), [5.59 (s), 5.56 (s) total 1 H, H<sub>8</sub>], 5.20 – 5.06 (2 H, m, H<sub>12</sub>), [4.85 (br d, *J* = 8.6 Hz), 4.72 (br s) total 1 H, H<sub>6</sub>], 3.56 – 3.30 (2 H, br m, H<sub>17a</sub>), [3.21 (app t, *J* = 9.1 Hz) and 2.74 – 1.88 (m) 1 H, H<sub>4</sub>], 2.74 – 1.88 (12 H, m, H<sub>2</sub>, H<sub>3</sub>, H<sub>5a</sub>, H<sub>17b</sub>, H<sub>18</sub>), 1.69 – 1.54 (1 H, m, H<sub>5b</sub>), [0.96 (s), 0.95 (s) total 9H, H<sub>10</sub>]; <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : [173.7, 172.6 (C<sub>7</sub>)], [159.4, 158.9 (C<sub>19</sub>)], [156.0, 155.8 (C<sub>11</sub>)], [151.9, 151.9], 140.3, 135.1, 132.4, [130.3, 130.3], 129.2, 129.2, 129.1, 129.0, 128.9, [127.2, 127.1], [126.0, 125.9], [125.2, 125.1], [124.6, 124.5], 122.8, 120.2, 119.5 (dd, *J* = 269.7, 288.4 Hz, C<sub>1</sub>), [96.3, 96.1 (C<sub>8</sub>)], [68.9, 68.8 (C<sub>12</sub>)], [65.8, 63.8 (C<sub>4</sub>)], [54.6, 53.7 (C<sub>6</sub>)], 52.7 (dd, *J* = 7.3, 23.3 Hz, H<sub>3</sub>), 48.6 – 48.2 (br m, C<sub>17</sub> and C<sub>18</sub>), 41.1 – 40.4 (m, C<sub>2a</sub>), 40.1 – 39.2 (m, C<sub>2b</sub>), 37.3 (C<sub>9</sub>), [34.3, 32.3 (C<sub>5</sub>)], [25.0, 25.0 (C<sub>10</sub>)]; <sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$ : –80.3 (d, *J* = 192.3 Hz), –80.5 (d, *J* = 192.3 Hz), –100.9 (br d, *J* = 192.8 Hz), –101.1 (br d, *J* = 191.2 Hz); *m/z* HRMS found [M + H]<sup>+</sup> 707.2805, C<sub>38</sub>H<sub>42</sub>ClF<sub>2</sub>N<sub>4</sub>O<sub>5</sub> requires 707.2806.

*1-(1-(2,2-diphenylethyl)cyclohexyl)pyrrolidine 688a*

Prepared according to general procedure B using 1-pyrrolidino-1-cyclohexene (32  $\mu$ l, 0.2 mmol) and 1,1-diphenylethene (72 mg, 0.4 mmol). The crude reaction mixture was filtered, the solvent removed *in vacuo* and subsequently dissolved in a solution of lithium hydroxide monohydrate (84 mg, 20 mmol) in tetrahydrofuran/water (6 mL, 5:1). The mixture was heated to a vigorous reflux for 2 hours, cooled to room temperature and diluted with saturated aqueous  $\text{NaHCO}_3$  (10 mL). The aqueous was extracted with ethyl acetate (3 x 10 mL) and the organics combined. The mixture was acidified using 10% HCl (aq) (25 mL), the organics separated and the aqueous washed with diethyl ether (2 x 20 mL). The aqueous was cooled in an ice bath and carefully basified using solid NaOH until pH = 10. The aqueous was extracted with dichloromethane (3 x 20 mL), the organics combined and washed with brine (25 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and the solvent removed *in vacuo*. The subsequent residue was purified by flash column chromatography (2% methanol in dichloromethane with 0.5%  $\text{Et}_3\text{N}$ ) to afford the product as a colourless oil (36 mg, 53%).  $R_f$  (25% ethyl acetate in petroleum ether): 0.25; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2932, 2856, 1649, 1597, 1492, 1449, 1349, 1263, 1155, 1077, 1030.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.32 (4 H, d,  $J = 7.7$  Hz,  $\text{H}_{10}$ ), 7.25 (4 H, d,  $J = 7.5$  Hz,  $\text{H}_{11}$ ), 7.13 (2 H, t,  $J = 6.4$  Hz,  $\text{H}_{12}$ ), 4.14 (1 H, t,  $J = 6.1$  Hz,  $\text{H}_8$ ), 2.60 (4 H, br t,  $\text{H}_5$ ), 2.26 (2 H, d,  $J = 6.1$  Hz,  $\text{H}_7$ ), 1.68 (4 H, br t,  $\text{H}_6$ ), 1.50 – 1.36 (5 H, m,  $\text{H}_{2a}$ ,  $\text{H}_{3a}$  and  $\text{H}_{4a}$ ), 1.30 – 1.16 (5 H, m,  $\text{H}_{2b}$ ,  $\text{H}_{3b}$  and  $\text{H}_{4b}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 147.4 ( $\text{C}_9$ ), 128.5 ( $\text{C}_{10}$ ), 128.0 ( $\text{C}_{11}$ ), 125.8 ( $\text{C}_{12}$ ), 56.9 ( $\text{C}_1$ ), 47.2 ( $\text{C}_8$ ), 44.0 ( $\text{C}_5$ ), 38.6 ( $\text{C}_7$ ), 33.7 ( $\text{C}_2$ ), 26.3 ( $\text{C}_4$ ), 24.5 ( $\text{C}_6$ ), 22.0 ( $\text{C}_3$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  334.2532,  $\text{C}_{24}\text{H}_{32}\text{N}$  requires 334.2529.

2-(2-(1-benzyl-4-(pyrrolidin-1-yl)piperidin-4-yl)-1-(4-chlorophenyl)ethyl)pyridine **688d**

Prepared according to general procedure B using *N*-benzyl-4-pyrrolidinyl-1,2,5,6-tetrahydropyridine **686d** (54 mg, 0.2 mmol) and 2-(1-(4-chlorophenyl)vinyl)pyridine **666ak** (86 mg, 0.4 mmol). The crude reaction mixture was purified by flash column chromatography (gradient elution: 10% ethyl acetate in dichloromethane with 0.5% Et<sub>3</sub>N to 2% methanol, 10% ethyl acetate in dichloromethane with 0.5% Et<sub>3</sub>N) to afford the product as a pale brown oil (waxy foam from hexane) (76 mg, 83%). *R<sub>f</sub>* (2% methanol, 10% ethyl acetate in dichloromethane): 0.11; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2944, 2811, 1637, 1587, 1568, 1488, 1471, 1452, 1432, 1409, 1366, 1343, 1151, 1090, 1014. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.53 (1 H, dq, *J* = 0.8, 4.9 Hz, H<sub>21</sub>), 7.51 (1 H, td, *J* = 1.9, 7.7 Hz, H<sub>19</sub>), 7.36 – 7.19 (9 H, m, H<sub>6</sub>, H<sub>7</sub>, H<sub>8</sub>, H<sub>14</sub>, H<sub>15</sub> and H<sub>18</sub>), 7.04 (1 H, ddd, *J* = 1.1, 4.8, 5.9 Hz, H<sub>20</sub>), 4.34 (1 H, br s, H<sub>12</sub>), 3.48 (2 H, br s, H<sub>4</sub>), 2.84 (1 H, br s, H<sub>11a</sub>), 2.61 (4 H, br s, H<sub>9</sub>), 2.44 (2 H, br s, H<sub>3a</sub>), 2.31 (2 H, br s, H<sub>3b</sub>), 2.08 (1 H, dd, *J* = 4.7, 14.6 Hz, H<sub>11b</sub>), 1.69 (4 H, br s, H<sub>10</sub>), 1.60 – 1.41 (4 H, br m, H<sub>2</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 164.2 (C<sub>17</sub>), 149.3 (C<sub>21</sub>), 144.7 (C<sub>13</sub>), 138.3 (br, C<sub>5</sub>), 136.6 (C<sub>19</sub>), 131.9 (C<sub>16</sub>), 129.4 (C<sub>6</sub> and C<sub>14</sub>), 128.6 (C<sub>15</sub>), 128.3 (C<sub>7</sub>), 127.2 (C<sub>8</sub>), 123.5 (C<sub>18</sub>), 121.3 (C<sub>20</sub>), 63.0 (C<sub>4</sub>), 55.5 (br, C<sub>1</sub>), 49.5 (C<sub>3</sub>), 48.0 (C<sub>12</sub>), 44.4 (C<sub>9</sub>), 37.6 (C<sub>11</sub>), 32.3 (C<sub>2a</sub>), 31.7 (C<sub>2b</sub>), 24.4 (C<sub>10</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 460.2507 {<sup>35</sup>Cl}, C<sub>29</sub>H<sub>35</sub>ClN<sub>3</sub> requires 460.2514 {<sup>35</sup>Cl}.

*(2S,4S)*-2-(*tert*-butyl)-3-Cbz-4-((1-morpholinocyclododecyl)methyl)oxazolidin-5-one **688e**

Prepared according to general procedure B using 1-morpholinocyclododecene (50.2 mg, 0.2 mmol) and (*S*)-2-(*tert*-butyl)-3-Cbz-4-methyleneoxazolidin-5-one **668** (62 mg, 0.22 mmol). The crude reaction mixture was purified by flash column chromatography (gradient elution: 100% petroleum ether to 20% ethyl acetate in petroleum ether) to afford the product as an amorphous white solid (65 mg, 60%).  $R_f$  (10% ethyl acetate in petroleum ether): 0.17; m.p. 68 – 72°C; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2937, 2850, 1788, 1715, 1455, 1389, 1323, 1299, 1225.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.38 – 7.33 (5 H, m,  $\text{H}_{19}$ ,  $\text{H}_{20}$  and  $\text{H}_{21}$ ), 5.58 (1 H, s,  $\text{H}_{13}$ ), 5.23 (1 H, d,  $J = 11.9$  Hz,  $\text{H}_{17a}$ ), 5.09 (1 H, d,  $J = 11.9$  Hz,  $\text{H}_{17b}$ ), 5.07 (1 H, t,  $J = 5.5$  Hz,  $\text{H}_{11}$ ), 3.56 (4 H, br s,  $\text{H}_9$ ), 2.81 – 2.76 (2 H, br m,  $\text{H}_{8a}$ ), 2.72 – 2.65 (2 H, br m,  $\text{H}_{8b}$ ), 1.90 (1 H, dd,  $J = 5.3, 15.4$  Hz,  $\text{H}_{10a}$ ), 1.77 (1 H, dd,  $J = 4.9, 15.4$  Hz,  $\text{H}_{10b}$ ), 1.52 – 1.17 (22 H, m,  $\text{H}_2$ ,  $\text{H}_3$ ,  $\text{H}_4$ ,  $\text{H}_5$ ,  $\text{H}_6$  and  $\text{H}_7$ ), 0.97 (9 H, s,  $\text{H}_{15}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 174.4 ( $\text{C}_{12}$ ), 156.6 ( $\text{C}_{16}$ ), 135.5 ( $\text{C}_{18}$ ), 128.8 (multiple C,  $\text{C}_{19}$ ,  $\text{C}_{20}$  and  $\text{C}_{21}$ ), 97.0 ( $\text{C}_{13}$ ), 68.6 ( $\text{C}_{17}$  and  $\text{C}_9$ ), 59.9 ( $\text{C}_1$ ), 53.5 ( $\text{C}_{11}$ ), 46.7 ( $\text{C}_8$ ), 41.1 ( $\text{C}_{10}$ ), 36.7 ( $\text{C}_{14}$ ), [27.1, 27.1, 26.2, 22.9, 22.8, 22.0, 21.9, 21.0, 20.9, (multiple C,  $\text{C}_2$ ,  $\text{C}_3$ ,  $\text{C}_4$ ,  $\text{C}_5$ ,  $\text{C}_6$  and  $\text{C}_7$ )], 25.4 ( $\text{C}_{15}$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  543.3812,  $\text{C}_{32}\text{H}_{51}\text{N}_2\text{O}_5$  requires 543.3792.



## 7 References

- (1) Nugent, T. C. *Chiral Amine Synthesis: Methods, Developments and Applications*; Wiley-VCH, 2010.
- (2) Cushnie, T. P. T.; Cushnie, B.; Lamb, A. J. *Int. J. Antimicrob. Agents* **2014**, *44*, 377–386.
- (3) Kittakoop, P.; Ruchirawat, C. M. and S. *Current Topics in Medicinal Chemistry*. 2014, pp 239–252.
- (4) Banks, W. A. *BMC Neurol.* **2009**, *9*, S3.
- (5) Mayol-Llinàs, J.; Nelson, A.; Farnaby, W.; Ayscough, A. *Drug Discov. Today* **2017**, *22*, 965–969.
- (6) Yu, L. F.; Zhang, H. K.; Caldarone, B. J.; Eaton, J. B.; Lukas, R. J.; Kozikowski, A. P. *J. Med. Chem.* **2014**, *57*, 8204–8223.
- (7) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451–3479.
- (8) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. *Nat. Chem.* **2018**, *10*, 383–394.
- (9) Brown, D. G.; Boström, J. *J. Med. Chem.* **2016**, *59*, 4443–4458.
- (10) Hoffmann, A. W. *Philos. Trans.* **1850**, *CXL*, 93.
- (11) Taylor, A. R.; Katritzky, R. J. K. In *Comprehensive Organic Functional Group Transformations II*; Elsevier: Oxford, 2005; pp 255–300.
- (12) Mitsunobu, O. *Comprehensive Organic Synthesis*, 6th ed.; Trost, B. M., Fleming, I., Ed.; Pergamon: Oxford, 1991.
- (13) Solomons, G., Fryhle, C. *Organic Chemistry*; Wiley: New York, 2000.
- (14) Walter, W., Beyer, H. *Handbook of Organic Chemistry*; Prentice Hall: New York, 1996.
- (15) Norman, R. O. C., Coxon, J. M. *Principles of Organic Syntheses*, 3rd ed.; Blackie Academic: New York, 1993.
- (16) Salvatore, R. N.; Nagle, A. S.; Jung, K. W. *J. Org. Chem.* **2002**, *67*, 674–683.
- (17) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.
- (18) Abdel-Magid, A. F.; Mehrman, S. J. *J. Org. Process Res. Dev.* **2006**, *10*, 971–1031.
- (19) Yagafarov, N. Z.; Kolesnikov, P. N.; Usanov, D. L.; Novikov, V. V.; Nelyubina, Y. V.; Chusov, D. *Chem. Commun.* **2016**, *52*, 1397–1400.
- (20) Szardenings, A. K.; Burkoth, T. S.; Look, G. C.; Campbell, D. A. *J. Org. Chem.* **1996**, *61*, 6720–6722.

- (21) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* **2011**, *111*, 1713–1760.
- (22) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916–4917.
- (23) Li, B.; Sortais, J.-B.; Darcel, C. *RSC Adv.* **2016**, *6*, 57603–57625.
- (24) Rueping, M.; Dufour, J.; Schoepke, F. R. *Green Chem.* **2011**, *13*, 1084.
- (25) Li, S.; Li, G.; Meng, W.; Du, H. *J. Am. Chem. Soc.* **2016**, *138*, 12956–12962.
- (26) Samec, J. S. M.; Bäckvall, J. E. *Chem. Eur. J.* **2002**, *8*, 2955–2961.
- (27) Volkov, A.; Tinnis, F.; Slagbrand, T.; Trillo, P.; Adolfsson, H. *Chem. Soc. Rev.* **2016**, *45*, 6685–6697.
- (28) Freifelder, M. *Practical Catalytic Hydrogenation*; Wiley- Interscience: New York, 1971.
- (29) Seyden-Penne, J. *Reductions by Alumino and Borohydrides in Organic Synthesis*, 2nd ed.; Wiley-VCH, 1997.
- (30) Saavedra, J. Z.; Resendez, A.; Rovira, A.; Eagon, S.; Haddenham, D.; Singaram, B. *J. Org. Chem.* **2012**, *77*, 221–228.
- (31) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1–48.
- (32) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29–41.
- (33) Cao, M.-H.; Green, N. J.; Xu, S.-Z. *Org. Biomol. Chem.* **2017**, *15*, 3105–3129.
- (34) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600–3740.
- (35) Wang, J.; Liu, X.; Feng, X. *Chem. Rev.* **2011**, *111*, 6947–6983.
- (36) Guerrero, C. A., Ryder, T. R. In *ACS Symposium Series, Vol. 1236*; 2016; pp 275–311.
- (37) Akiyama, T.; Mori, K. *Chem. Rev.* **2015**, *115*, 9277–9306.
- (38) Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books, 2010.
- (39) Hansen, K. B.; Hsiao, Y.; Xu, F.; Rivera, N.; Clausen, A.; Kubryk, M.; Krska, S.; Rosner, T.; Simmons, B.; Balsells, J.; Ikemoto, N.; Sun, Y.; Spindler, F.; Malan, C.; Grabowski, E. J. J.; Armstrong, J. D. *J. Am. Chem. Soc.* **2009**, *131*, 8798–8804.
- (40) Savile, C. K.; Janey, J. M.; Mundorff, E. C.; Moore, J. C.; Tam, S.; Jarvis, W. R.; Colbeck, J. C.; Krebber, A.; Fleitz, F. J.; Brands, J.; Devine, P. N.; Huisman, G. W.; Hughes, G. J. *Science* **2010**, *329*, 305–309.
- (41) Kelly, S. A.; Pohle, S.; Wharry, S.; Mix, S.; Allen, C. C. R.; Moody, T. S.; Gilmore, B. F. *Chem. Rev.* **2018**, *118*, 349–367.
- (42) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785–7811.
- (43) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673–686.

- (44) Reznichenko, A. L.; Nguyen, H. N.; Hultzs, K. C. *Angew. Chem. Int. Ed.* **2010**, *49*, 8984–8987.
- (45) Manna, K.; Xu, S.; Sadow, A. D. *Angew. Chem. Int. Ed.* **2011**, *50*, 1865–1868.
- (46) Gribkov, D. V.; Hultzs, K. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 5542–5546.
- (47) Knight, P. D.; Munslow, I.; O'Shaughnessy, P. N.; Scott, P. *Chem. Commun.* **2004**, 894–895.
- (48) Wood, M. C.; Leitch, D. C.; Yeung, C. S.; Kozak, J. A.; Schafer, L. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 354–358.
- (49) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175–4178.
- (50) Shapiro, N. D.; Rauniyar, V.; Hamilton, G. L.; Wu, J.; Toste, F. D. *Nature* **2011**, *470*, 245–250.
- (51) Martinez, P. H.; Hultzs, K. C.; Hampel, F. *Chem. Commun.* **2006**, 2221–2223.
- (52) Ogata, T.; Ujihara, A.; Tsuchida, S.; Shimizu, T.; Kaneshige, A.; Tomioka, K. *Tetrahedron Lett.* **2007**, *48*, 6648–6650.
- (53) Müller, T. E.; Hultzs, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795–3892.
- (54) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. *Chem. Rev.* **2015**, *115*, 2596–2697.
- (55) Ambühl, J.; Pregosin, P. S.; Venanzi, L. M.; Ughetto, G.; Zambonelli, L. *Angew. Chem. Int. Ed.* **1975**, *14*, 369.
- (56) Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070–1071.
- (57) Bender, C. F.; Brown, T. J.; Widenhoefer, R. A. *Organometallics* **2016**, *35*, 113–125.
- (58) Liu, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 1570–1571.
- (59) Julian, L. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 13813–13822.
- (60) Shen, X.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2010**, *49*, 564–567.
- (61) Michon, C.; Abadie, M. A.; Medina, F.; Agbossou-Niedercorn, F. *Catal. Today* **2014**, *235*, 2–13.
- (62) Kojima, M.; Mikami, K. *Synlett* **2012**, 57–61.
- (63) Baumann, M.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2265–2319.
- (64) Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 6042–6043.
- (65) Lutete, L. M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622–1623.
- (66) Schuster, H. F.; Coppola, G. M. *Allenenes in Organic Synthesis*; Wiley-Interscience: New York, 1984.
- (67) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994–2009.

- (68) Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 2887–2889.
- (69) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452–2453.
- (70) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. **2007**, *121*.
- (71) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Herwig, J.; Müller T, E.; Thiel O, R. *Chem. Eur. J.* **1999**, *5*, 1306–1319.
- (72) Beller, M.; Eichberger, M.; Trauthwein, H. *Angew. Chem. Int. Ed.* **1997**, *36*, 2225–2227.
- (73) Utsunomiya, M.; Kuwano, R.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 5608–5609.
- (74) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 2702–2703.
- (75) Takaya, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 5756–5757.
- (76) Otsuka, M.; Yokoyama, H.; Endo, K.; Shibata, T. *Org. Biomol. Chem.* **2012**, *10*, 3815–3818.
- (77) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546–9547.
- (78) Nettekoven, U.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1166–1167.
- (79) Li, K.; Horton, P. N.; Hursthouse, M. B.; Hii, K. K. M. *J. Organomet. Chem.* **2003**, *665*, 250–257.
- (80) Hu, A.; Ogasawara, M.; Sakamoto, T.; Okada, A.; Nakajima, K.; Takahashi, T.; Lin, W. *Adv. Synth. Catal.* **2006**, *348*, 2051–2056.
- (81) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14286–14287.
- (82) Pawlas, J.; Nakao, Y.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 3669–3679.
- (83) Minami, T.; Okamoto, H.; Ikeda, S.; Tanaka, R.; Ozawa, F.; Yoshifuji, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 4501–4503.
- (84) Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828–1839.
- (85) Yi, C. S.; Yun, S. Y. *Org. Lett.* **2005**, *7*, 2181–2183.
- (86) Löber, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366–4367.
- (87) Hodjat-Kachani, H.; Perie, J. J.; Lattes, A. *Chem. Lett.* **1976**, *5*, 405.
- (88) Al-Masum, M.; Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 6071–6074.
- (89) Kuchenbeiser, G.; Shaffer, A. R.; Zingales, N. C.; Beck, J. F.; Schmidt, J. A. R. *J. Organomet. Chem.* **2011**, *696*, 179–187.
- (90) Beck, J. F.; Schmidt, J. A. R. *RSC Adv.* **2012**, *2*, 128–131.
- (91) Beck, J. F.; Samblanet, D. C.; Schmidt, J. A. R. *RSC Adv.* **2013**, *3*, 20708.
- (92) Zingales, N. C.; Shaffer, A. R.; Schmidt, J. A. R. *Organometallics* **2013**, *32*, 578–586.

- (93) Nishina, N.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 3314–3317.
- (94) Nishina, N.; Yamamoto, Y. *Tetrahedron* **2009**, *65*, 1799–1808.
- (95) Kinder, R. E.; Zhang, Z.; Widenhoefer, R. A. *Org. Lett.* **2008**, *10*, 3157–3159.
- (96) Butler, K. L.; Tragni, M.; Widenhoefer, R. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 5175–5178.
- (97) Cooke, M. L.; Xu, K.; Breit, B. *Angew. Chem. Int. Ed.* **2012**, *51*, 10876–10879.
- (98) Xu, K.; Thieme, N.; Breit, B. *Angew. Chem. Int. Ed.* **2014**, *53*, 2162–2165.
- (99) Changkun, L.; Matthias, K.; Bernhard, B. *Angew. Chem. Int. Ed.* **2014**, *53*, 13780–13784.
- (100) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738–6744.
- (101) Dorta, R.; Egli, P.; Zürcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857–10858.
- (102) Zhou, J. (Steve); Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220–12221.
- (103) Ickes, A. R.; Ensign, S. C.; Gupta, A. K.; Hull, K. L. *J. Am. Chem. Soc.* **2014**, *136*, 11256–11259.
- (104) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 10830–10834.
- (105) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746–15749.
- (106) Pirnot, M. T.; Wang, Y. M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 48–57.
- (107) Zhu, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 15913–15916.
- (108) Niljianskul, N.; Zhu, S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 1638–1641.
- (109) Yang, Y.; Shi, S. L.; Niu, D.; Liu, P.; Buchwald, S. L. *Science* **2015**, *349*, 62–66.
- (110) Shi, S. L.; Buchwald, S. L. *Nat. Chem.* **2015**, *7*, 38–44.
- (111) Shi, S. L.; Wong, Z. L.; Buchwald, S. L. *Nature* **2016**, *532*, 353–356.
- (112) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *Nat. Chem.* **2016**, *8*, 144–150.
- (113) Wang, H.; Yang, J. C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2017**, *139*, 8428–8431.
- (114) Gui, J.; Pan, C.; Jin, Y.; Qin, T.; Lo, J. C.; Lee, B. J.; Spergel, S. H.; Mertzman, M. E.; Pitts, W. J.; Cruz, T. E. L.; Schmidt, M. A.; Darvatkar, N.; Natarajan, S. R.; Baran, P. S. *Science* **2015**, *348*, 415–421.
- (115) Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Rüttinger, R.; Kojer, H. *Angew. Chem.* **1959**, *71*, 176–182.
- (116) Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A. *Angew. Chem. Int. Ed.* **1962**, *1*, 80–88.
- (117) Åkermark, B.; E. Bäckvall, J.; Siirala-Hanseñ, K.; Sjöberg, K.; Zetterberg, K. *Tetrahedron Lett.* **1974**, *15*, 1363–1366.
- (118) Baeckvall, J. E. *Acc. Chem. Res.* **1983**, *16*, 335–342.
- (119) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981–3019.
- (120) Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.*

- 2005**, 127, 2868–2869.
- (121) Hanley, P. S.; Marković, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, 132, 6302–6303.
- (122) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, 36, 1142–1152.
- (123) Ney, J. E.; Wolfe, J. P. *Angew. Chem. Int. Ed.* **2004**, 43, 3605–3608.
- (124) Bertrand, M. B.; Neukom, J. D.; Wolfe, J. P. *J. Org. Chem.* **2008**, 73, 8851–8860.
- (125) Mai, D. N.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, 132, 12157–12159.
- (126) Rönn, M.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett.* **1995**, 36, 7749–7752.
- (127) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, 61, 3584–3585.
- (128) Fix, S. R.; Brice, J. R.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2002**, 41, 164–166.
- (129) Kohler, D. G.; Gockel, S. N.; Kennemur, J. L.; Waller, P. J.; Hull, K. L. *Nat. Chem.* **2018**, 10, 333–340.
- (130) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, 127, 7690–7691.
- (131) Lei, A.; Lu, X.; Liu, G. *Tetrahedron Lett.* **2004**, 45, 1785–1788.
- (132) Wu, T.; Yin, G.; Liu, G. *J. Am. Chem. Soc.* **2009**, 131, 16354–16355.
- (133) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, 127, 14586–14587.
- (134) He, W.; Yip, K.-T.; Zhu, N.-Y.; Yang, D. *Org. Lett.* **2009**, 11, 5626–5628.
- (135) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z. *J. Am. Chem. Soc.* **1988**, 110, 3994–4002.
- (136) Shinohara, T.; Arai, M. A.; Wakita, K.; Arai, T.; Sasai, H. *Tetrahedron Lett.* **2003**, 44, 711–714.
- (137) Tsujihara, T.; Shinohara, T.; Takenaka, K.; Takizawa, S.; Onitsuka, K.; Hatanaka, M.; Sasai, H. *J. Org. Chem.* **2009**, 74, 9274–9279.
- (138) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2008**, 130, 8590–8591.
- (139) Desai, L. V.; Sanford, M. S. *Angew. Chem. Int. Ed.* **2007**, 46, 5737–5740.
- (140) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, 128, 7179–7181.
- (141) Race, N. J.; Hazelden, I. R.; Faulkner, A.; Bower, J. F. *Chem. Sci.* **2017**, 8, 5248–5260.
- (142) Tsutsui, H.; Narasaka, K. *Chem. Lett.* **1999**, 28, 45–46.
- (143) Fürstner, A.; Radkowski, K.; Peters, H. *Angew. Chem. Int. Ed.* **2005**, 44, 2777–2781.
- (144) Nishimura, T.; Nishiguchi, Y.; Maeda, Y.; Uemura, S. *J. Org. Chem.* **2004**, 69, 5342–5347.
- (145) Faulkner, A.; Scott, J. S.; Bower, J. F. *J. Am. Chem. Soc.* **2015**, 137, 7224–7230.
- (146) Hazelden, I. R.; Ma, X.; Langer, T.; Bower, J. F. *Angew. Chem. Int. Ed.* **2016**, 55, 11198–11202.

- (147) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001–1020.
- (148) Crozet, D.; Urrutigoity, M.; Kalck, P. *ChemCatChem* **2011**, *3*, 1102–1118.
- (149) Chen, C.; Dong, X.-Q.; Zhang, X. *Org. Chem. Front.* **2016**, *3*, 1359–1370.
- (150) Kalck, P.; Urrutigoity, M. *Chem. Rev.* **2018**, *118*, 3833–3861.
- (151) Walter, R.; Hellmuth, V. *Justus Liebigs Ann. Chem.* **1953**, 582, 133–161.
- (152) Iqbal, A. F. M. *Helv. Chim. Acta* **1971**, *54*, 1440–1445.
- (153) Kranemann, C. L.; Eilbracht, P. *Synthesis* **1998**, *1*, 71–77.
- (154) Kranemann, C. L.; Kitsos-Rzychon, B. E.; Eilbracht, P. *Tetrahedron* **1999**, *55*, 4721–4732.
- (155) Kranemann, C. L.; Eilbracht, P. *Eur. J. Org. Chem.* **2000**, 2367–2377.
- (156) Schmidt, A.; Marchetti, M.; Eilbracht, P. *Tetrahedron* **2004**, *60*, 11487–11492.
- (157) Zimmermann, B.; Herwig, J.; Beller, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 2372–2375.
- (158) Briggs, J. R.; Klosin, J.; Whiteker, G. T. *Org. Lett.* **2005**, *7*, 4795–4798.
- (159) Oliveira, K. C. B.; Carvalho, S. N.; Duarte, M. F.; Gusevskaya, E. V.; dos Santos, E. N.; Karroumi, J. El; Gouygou, M.; Urrutigoity, M. *Appl. Catal. A Gen.* **2015**, *497*, 10–16.
- (160) Fuentes, J. A.; Wawrzyniak, P.; Roff, G. J.; Buhl, M.; Clarke, M. L. *Catal. Sci. Technol.* **2011**, *1*, 431–436.
- (161) Seayad, A.; Ahmed, M.; Klein, H.; Jackstell, R.; Gross, T.; Beller, M. *Science* **2002**, *297*, 1676–1678.
- (162) Ahmed, M.; Seayad, A. M.; Jackstell, R.; Beller, M. *J. Am. Chem. Soc.* **2003**, *125*, 10311–10318.
- (163) Ahmed, M.; Bronger, R. P. J.; Jackstell, R.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M.; Beller, M. *Chem. Eur. J.* **2006**, *12*, 8979–8988.
- (164) Ahlers, W.; Paciello, D.; Vogt, D.; Hofmann, P. WO 02/083695A1, 2002.
- (165) Guodu, L.; Kexuan, H.; Chaoxian, C.; Bonan, C.; Mingxin, C.; Wenjun, W.; Xumu, Z. *Chem. Eur. J.* **2011**, *17*, 14559–14563.
- (166) Liu, G.; Huang, K.; Cao, B.; Chang, M.; Li, S.; Yu, S.; Zhou, L.; Wu, W.; Zhang, X. *Org. Lett.* **2012**, *14*, 102–105.
- (167) Botteghi, C.; Cazzolato, L.; Marchetti, M.; Paganelli, S. *J. Org. Chem.* **1995**, *60*, 6612–6615.
- (168) Routaboul, L.; Buch, C.; Klein, H.; Jackstell, R.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 7401–7405.
- (169) Li, S.; Huang, K.; Zhang, J.; Wu, W.; Zhang, X. *Org. Lett.* **2013**, *15*, 3078–3081.
- (170) Seayad, A. M.; Selvakumar, K.; Ahmed, M.; Beller, M. *Tetrahedron Lett.* **2003**, *44*, 1679–1683.
- (171) Ahmed, M.; Buch, C.; Routaboul, L.; Jackstell, R.; Klein, H.; Spannenberg, A.; Beller, M.

- Chem. Eur. J.* **2007**, *13*, 1594–1601.
- (172) Li, S.; Huang, K.; Zhang, J.; Wu, W.; Zhang, X. *Org. Lett.* **2013**, *15*, 1036–1039.
- (173) Crozet, D.; Kefalidis, C. E.; Urrutigoñty, M.; Maron, L.; Kalck, P. *ACS Catal.* **2014**, *4*, 435–447.
- (174) Villa-Marcos, B.; Xiao, J. *Chinese J. Catal.* **2015**, *36*, 106–112.
- (175) Meng, J.; Li, X.-H.; Han, Z.-Y. *Org. Lett.* **2017**, *19*, 1076–1079.
- (176) Chen, C.; Jin, S.; Zhang, Z.; Wei, B.; Wang, H.; Zhang, K.; Lv, H.; Dong, X.-Q.; Zhang, X. *J. Am. Chem. Soc.* **2016**, *138*, 9017–9020.
- (177) Townes, J. A.; Evans, M. A.; Queffelec, J.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2002**, *4*, 2537–2540.
- (178) Muraoka, T.; Kamiya, S.; Matsuda, I.; Itoh, K. *Chem. Commun.* **2002**, 1284–1285.
- (179) Du, Y.; Xu, L.-W.; Shimizu, Y.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 16146–16147.
- (180) Trost, B. M.; Silverman, S. M. *J. Am. Chem. Soc.* **2010**, *132*, 8238–8240.
- (181) Skucas, E.; Ngai, M. Y.; Komanduri, V.; Krische, M. J. *Acc. Chem. Res.* **2007**, *40*, 1394–1401.
- (182) Xie, M.; Liu, X.; Zhu, Y.; Zhao, X.; Xia, Y.; Lin, L.; Feng, X. *Chem. Eur. J.* **2011**, *17*, 13800–13805.
- (183) Kimura, M.; Miyachi, A.; Kojima, K.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2004**, *126*, 14360–14361.
- (184) Komanduri, V.; Grant, C. D.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 12592–12593.
- (185) Perez, F.; Oda, S.; Geary, L. M.; Krische, M. J. *Top. Curr. Chem.* **2016**, *374*, 1–23.
- (186) Chen, T.-Y.; Tsutsumi, R.; Montgomery, T. P.; Volchkov, I.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 1798–1801.
- (187) Oda, S.; Sam, B.; Krische, M. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 8525–8528.
- (188) Oda, S.; Franke, J.; Krische, M. J. *Chem. Sci.* **2016**, *7*, 136–141.
- (189) Yang, Y.; Perry, I. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 9787–9790.
- (190) Smith, P. A. *Nitrenes*, Interscien.; Lwowski, W., Ed.; 1970.
- (191) ApSimon, J. W.; Edwards, O. E. *Can. J. Chem.* **1962**, *40*, 896–902.
- (192) Kwart, H.; Khan, A. A. *J. Am. Chem. Soc.* **1967**, *89*, 1951–1953.
- (193) Breslow, R.; Gellman, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 6728–6729.
- (194) Mansuy, D.; Mahy, J.-P.; Dureault, A.; Bedi, G.; Battioni, P. *J. Chem. Soc., Chem. Commun.* **1984**, 1161–1163.
- (195) Park, Y.; Kim, Y.; Chang, S. *Chem. Rev.* **2017**, *117*, 9247–9301.



- (196) Rit, R. K.; Shankar, M.; Sahoo, A. K. *Org. Biomol. Chem.* **2017**, *15*, 1282–1293.
- (197) Hazelard, D.; Nocquet, P.-A.; Compain, P. *Org. Chem. Front.* **2017**, 2500–2521.
- (198) Guthikonda, K.; Wehn, P. M.; Caliendo, B. J.; Du Bois, J. *Tetrahedron* **2006**, *62*, 11331–11342.
- (199) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233–2236.
- (200) Liu, Y.; Che, C. *Chem. Eur. J.* **2010**, *16*, 10494–10501.
- (201) Paradine, S. M.; White, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 2036–2039.
- (202) Ragaini, F.; Penoni, A.; Gallo, E.; Tollari, S.; Li Gotti, C.; Lapadula, M.; Mangioni, E.; Cenini, S. *Chem. Eur. J.* **2003**, *9*, 249–259.
- (203) Paradine, S. M.; Griffin, J. R.; Zhao, J.; Petronico, A. L.; Miller, S. M.; White, C. M. *Nat. Chem.* **2015**, *7*, 987–994.
- (204) King, E. R.; Hennessy, E. T.; Betley, T. A. *J. Am. Chem. Soc.* **2011**, *133*, 4917–4923.
- (205) Iovan, D. A.; Betley, T. A. *J. Am. Chem. Soc.* **2016**, *138*, 1983–1993.
- (206) Roizen, J. L.; Harvey, M. E.; Bois, J. Du. *Acc. Chem. Res.* **2012**, *45*, 911–922.
- (207) Fiori, K. W.; Espino, C. G.; Brodsky, B. H.; Du Bois, J. *Tetrahedron* **2009**, *65*, 3042–3051.
- (208) Zhang, X.; Ke, Z.; Deyonker, N. J.; Xu, H.; Li, Z. F.; Xu, X.; Zhang, X.; Su, C. Y.; Phillips, D. L.; Zhao, C. *J. Org. Chem.* **2013**, *78*, 12460–12468.
- (209) Perry, R. H.; Cahill, T. J.; Roizen, J. L.; Du Bois, J.; Zare, R. N. *Proc. Natl. Acad. Sci.* **2012**, *109*, 18295–18299.
- (210) Xu, H.; Zhang, X.; Ke, Z.; Zhao, C. *RSC Adv.* **2016**, *6*, 29045–29053.
- (211) Espino, C. G.; Du Bois, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 598–600.
- (212) Du Bois, J. *Org. Process Res. Dev.* **2011**, *15*, 758–762.
- (213) Wehn, P. M.; Lee, J.; Du Bois, J. *Org. Lett.* **2003**, *5*, 4823–4826.
- (214) Darses, B.; Rodrigues, R.; Neuville, L.; Mazurais, M.; Dauban, P. *Chem. Commun.* **2017**, *53*, 493–508.
- (215) Fleming, J. J.; McReynolds, M. D.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 9964–9975.
- (216) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510–11511.
- (217) Zalatan, D. N.; Du Bois, J. *J. Am. Chem. Soc.* **2009**, *131*, 7558–7559.
- (218) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378–15379.
- (219) Kurokawa, T.; Kim, M.; Du Bois, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 2777–2779.
- (220) Grigg, R. D.; Rigoli, J. W.; Pearce, S. D.; Schomaker, J. M. *Org. Lett.* **2012**, *14*, 280–283.
- (221) Nguyen, Q.; Sun, K.; Driver, T. G. *J. Am. Chem. Soc.* **2012**, *134*, 7262–7265.
- (222) Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 562–568.
- (223) Roizen, J. L.; Zalatan, D. N.; Du Bois, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 11343–11346.

- (224) Chiappini, N. D.; Mack, J. B. C.; Du Bois, J. *Angew. Chem. Int. Ed.* **2018**, 5050–5053.
- (225) Bess, E. N.; DeLuca, R. J.; Tindall, D. J.; Oderinde, M. S.; Roizen, J. L.; Du Bois, J.; Sigman, M. S. *J. Am. Chem. Soc.* **2014**, 136, 5783–5789.
- (226) Liang, C.; Robert-Peillard, F.; Fruit, C.; Müller, P.; Dodd, R. H.; Dauban, P. *Angew. Chem. Int. Ed.* **2006**, 45, 4641–4644.
- (227) Liang, C.; Collet, F.; Robert-Peillard, F.; Müller, P.; Dodd, R. H.; Dauban, P. *J. Am. Chem. Soc.* **2008**, 130, 343–350.
- (228) Lebel, H.; Spitz, C.; Leogane, O.; Trudel, C.; Parmentier, M. *Org. Lett.* **2011**, 13, 5460–5463.
- (229) Lebel, H.; Trudel, C.; Spitz, C. *Chem. Commun.* **2012**, 48, 7799–7801.
- (230) Reddy, R. P.; Davies, H. M. L. *Org. Lett.* **2006**, 8, 5013–5016.
- (231) Zalatan, D. N.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, 130, 9220–9221.
- (232) Watanabe, N.; Matsuda, H.; Kuribayashi, H.; Hashimoto, S.-I. *Heterocycles* **1996**, 42, 537–542.
- (233) Cui, Y.; He, C. *Angew. Chem. Int. Ed.* **2004**, 43, 4210–4212.
- (234) Li, Z.; Capretto, D. A.; Rahaman, R.; He, C. *Angew. Chem. Int. Ed.* **2007**, 46, 5184–5186.
- (235) Rigoli, J. W.; Weatherly, C. D.; Alderson, J. M.; Vo, B. T.; Schomaker, J. M. *J. Am. Chem. Soc.* **2013**, 135, 17238–17241.
- (236) Alderson, J. M.; Phelps, A. M.; Scamp, R. J.; Dolan, N. S.; Schomaker, J. M. *J. Am. Chem. Soc.* **2014**, 136, 16720–16723.
- (237) Sun, K.; Sachwani, R.; Richert, K. J.; Driver, T. G. *Org. Lett.* **2009**, 11, 3598–3601.
- (238) Ichinose, M.; Suematsu, H.; Yasutomi, Y.; Nishioka, Y.; Uchida, T.; Katsuki, T. *Angew. Chem. Int. Ed.* **2011**, 50, 9884–9887.
- (239) Zhang, Y.; Feng, B.; Zhu, C. *Org. Biomol. Chem.* **2012**, 10, 9137–9141.
- (240) Nishioka, Y.; Uchida, T.; Katsuki, T. *Angew. Chem. Int. Ed.* **2013**, 52, 1739–1742.
- (241) Hong, S. Y.; Park, Y.; Hwang, Y.; Kim, Y. B.; Baik, M.; Chang, S. *Science* **2018**, 359, 1016–1021.
- (242) Dydio, P.; Key, H. M.; Hayashi, H.; Clark, D. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2017**, 139, 1750–1753.
- (243) Prier, C. K.; Zhang, R. K.; Buller, A. R.; Brinkmann-Chen, S.; Arnold, F. H. *Nat. Chem.* **2017**, 9, 629–634.
- (244) Kharasch, M. S.; Sosnovsky, G. *J. Am. Chem. Soc.* **1958**, 80, 756.
- (245) Kharasch, M. S.; Sosnovsky, G.; Yang, N. C. *J. Am. Chem. Soc.* **1959**, 81, 5819–5824.
- (246) Ni, Z.; Zhang, Q.; Xiong, T.; Zheng, Y.; Li, Y.; Zhang, H.; Zhang, J.; Liu, Q. *Angew. Chem.*

- Int. Ed.* **2012**, *51*, 1244–1247.
- (247) Kohmura, Y.; Kawasaki, K.; Katsuki, T. *Synlett* **1997**, *12*, 1456–1458.
- (248) Wiese, S.; Badiei, M. Y.; Gephart, T. R.; Mossin, S.; Varonka, S. M.; Melzer, M. M.; Meyer, K.; Cundari, R. T.; Warren, T. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 8850–8855.
- (249) Gephart III, R. T.; Huang, D. L.; Aguila, M. J. B.; Schmidt, G.; Shahu, A.; Warren, T. H. *Angew. Chem. Int. Ed.* **2012**, *51*, 6488–6492.
- (250) Michaudel, Q.; Thevenet, D.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 2547–2550.
- (251) Tran, B. L.; Li, B.; Driess, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 2555–2563.
- (252) Sharma, A.; Hartwig, J. F. *Nature* **2015**, *517*, 600–604.
- (253) Karimov, R. R.; Sharma, A.; Hartwig, J. F. *ACS Cent. Sci.* **2016**, *2*, 715–724.
- (254) Lee, M.; Sanford, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 12796–12799.
- (255) Lee, M.; Sanford, M. S. *Org. Lett.* **2017**, *19*, 572–575.
- (256) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900–2936.
- (257) Lyons, T.; Sanford, M. *Chem. Rev.* **2010**, 1147–1169.
- (258) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. *Chem. Rev.* **2017**, *117*, 8754–8786.
- (259) Cope, A. C.; Siekman, R. W. *J. Am. Chem. Soc.* **1965**, *87*, 3272–3273.
- (260) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527–2571.
- (261) Wasa, M.; Chan, K. S. L.; Zhang, X. G.; He, J.; Miura, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 18570–18572.
- (262) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048–9049.
- (263) Kang, T.; Kim, Y.; Lee, D.; Wang, Z.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 4141–4144.
- (264) He, J.; Shigenari, T.; Yu, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 6545–6549.
- (265) Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 1248–1250.
- (266) Li, Y.; Li, B.; Wang, W.; Huang, W.; Zhang, X.; Chen, K.; Shi, Z. *Angew. Chem. Int. Ed.* **2011**, *50*, 2115–2119.
- (267) Li, Y.; Zhang, X.-S.; Li, H.; Wang, W.-H.; Chen, K.; Li, B.-J.; Shi, Z.-J. *Chem. Sci.* **2012**, *3*, 1634–1639.
- (268) Li, Y.; Zhang, X.-S.; Zhu, Q.-L.; Shi, Z.-J. *Org. Lett.* **2012**, *14*, 4498–4501.
- (269) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650–3651.
- (270) Tran, D. N.; Cramer, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 8181–8184.
- (271) Tran, D. N.; Cramer, N. *Angew. Chem. Int. Ed.* **2011**, *50*, 11098–11102.

- (272) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141–5143.
- (273) Hummel, J. R.; Ellman, J. A. *Isr. J. Chem.* **2017**, *57*, 916–931.
- (274) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407–1438.
- (275) Wangweerawong, A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2014**, *136*, 8520–8523.
- (276) Wangweerawong, A.; Hummel, J. R.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2016**, *81*, 1547–1557.
- (277) Best, D.; Kujawa, S.; Lam, H. W. *J. Am. Chem. Soc.* **2012**, *134*, 18193–18196.
- (278) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155.
- (279) He, G.; Chen, G. *Angew. Chem. Int. Ed.* **2011**, *50*, 5192–5196.
- (280) Cui, W.; Chen, S.; Wu, J.-Q.; Zhao, X.; Hu, W.; Wang, H. *Org. Lett.* **2014**, *16*, 4288–4291.
- (281) Fan, Z.; Shu, S.; Ni, J.; Yao, Q.; Zhang, A. *ACS Catal.* **2016**, *6*, 769–774.
- (282) Wang, H.; Tong, H. R.; He, G.; Chen, G. *Angew. Chem. Int. Ed.* **2016**, *55*, 15387–15391.
- (283) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124–2127.
- (284) Zhang, L.; Chen, G.; Wang, X.; Guo, Q.; Zhang, X.; Pan, F.; Chen, K.; Shi, Z. *Angew. Chem. Int. Ed.* **2014**, *53*, 3899–3903.
- (285) Xu, J.-W.; Zhang, Z.-Z.; Rao, W.-H.; Shi, B.-F. *J. Am. Chem. Soc.* **2016**, *138*, 10750–10753.
- (286) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7–10.
- (287) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3–6.
- (288) Zhao, J.; Zhao, X.-J.; Cao, P.; Liu, J.-K.; Wu, B. *Org. Lett.* **2017**, *19*, 4880–4883.
- (289) Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313–7316.
- (290) Rodriguez, N.; Romero-Revilla, J. A.; Fernandez-Ibanez, M. A.; Carretero, J. C. *Chem. Sci.* **2013**, *4*, 175–179.
- (291) Poveda, A.; Alonso, I.; Fernandez-Ibanez, M. A. *Chem. Sci.* **2014**, *5*, 3873–3882.
- (292) Hernando, E.; Villalva, J.; Martínez, Á. M.; Alonso, I.; Rodríguez, N.; Gómez Arrayás, R.; Carretero, J. C. *ACS Catal.* **2016**, *6*, 6868–6882.
- (293) Wang, C.; Zhang, L.; Chen, C.; Han, J.; Yao, Y.; Zhao, Y. *Chem. Sci.* **2015**, *6*, 4610–4614.
- (294) Han, J.; Zheng, Y.; Wang, C.; Zhu, Y.; Shi, D.-Q.; Zeng, R.; Huang, Z.-B.; Zhao, Y. *J. Org. Chem.* **2015**, *80*, 9297–9306.
- (295) Han, J.; Zheng, Y.; Wang, C.; Zhu, Y.; Huang, Z.-B.; Shi, D.-Q.; Zeng, R.; Zhao, Y. *J. Org. Chem.* **2016**, *81*, 5681–5689.
- (296) Fan, M.; Ma, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 12152–12155.

- (297) Peng-Xiang, L.; Sheng-Long, F.; Xue-Song, Y.; Kai, C.; Bo-Zheng, S.; Bing-Feng, S. *Chem. Eur. J.* **2015**, *21*, 17503–17507.
- (298) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965–3972.
- (299) He, G.; Zhang, S.-Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem. Int. Ed.* **2013**, *52*, 11124–11128.
- (300) Wang, Z.; Ni, J.; Kuninobu, Y.; Kanai, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 3496–3499.
- (301) Wu, X.; Zhao, Y.; Zhang, G.; Ge, H. *Angew. Chem. Int. Ed.* **2014**, *53*, 3706–3710.
- (302) Wu, X.; Zhao, Y.; Ge, H. *Chem. Eur. J.* **2014**, *20*, 9530–9533.
- (303) Wu, X.; Yang, K.; Zhao, Y.; Sun, H.; Li, G.; Ge, H. *Nat. Commun.* **2015**, *6*, 1–10.
- (304) Zhang, J.; Chen, H.; Lin, C.; Liu, Z.; Wang, C.; Zhang, Y. *J. Am. Chem. Soc.* **2015**, *137*, 12990–12996.
- (305) Williamson, P.; Galvan, A.; Gaunt, M. *J. Chem. Sci.* **2017**, *8*, 2588–2591.
- (306) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788–802.
- (307) Chan, K. S. L.; Wasa, M.; Chu, L.; Laforteza, B. N.; Miura, M.; Yu, J.-Q. *Nat. Chem.* **2014**, *6*, 146–150.
- (308) Cheng, G.-J.; Yang, Y.-F.; Liu, P.; Chen, P.; Sun, T.-Y.; Li, G.; Zhang, X.; Houk, K. N.; Yu, J.-Q.; Wu, Y.-D. *J. Am. Chem. Soc.* **2014**, *136*, 894–897.
- (309) Chan, K. S. L.; Fu, H.-Y.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 2042–2046.
- (310) Jiang, H.; He, J.; Liu, T.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 2055–2059.
- (311) Shao, Q.; He, J.; Wu, Q.-F.; Yu, J.-Q. *ACS Catal.* **2017**, *7*, 7777–7782.
- (312) Shao, Q.; Wu, Q.-F.; He, J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2018**, *140*, 5322–5325.
- (313) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074.
- (314) Herzon, S. B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 6690–6691.
- (315) Herzon, S. B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 14940–14941.
- (316) Eisenberger, P.; Ayinla, R. O.; Lauzon, J. M. P.; Schafer, L. L. *Angew. Chem. Int. Ed.* **2009**, *48*, 8361–8365.
- (317) Kubiak, R.; Prochnow, I.; Doye, S. *Angew. Chem. Int. Ed.* **2008**, *48*, 1153–1156.
- (318) Bexrud, J. A.; Eisenberger, P.; Leitch, D. C.; Payne, P. R.; Schafer, L. L. *J. Am. Chem. Soc.* **2009**, *131*, 2116–2118.
- (319) Jun, C.-H. *Chem. Commun.* **1998**, 1405–1406.
- (320) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935–10941.
- (321) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220–14221.

- (322) Prokopcová, H.; Bergman, S. D.; Aelvoet, K.; Smout, V.; Herrebout, W.; Van der Veken, B.; Meerpoel, L.; Maes, B. U. V. *Chem. Eur. J.* **2010**, *16*, 13063–13067.
- (323) Dastbaravardeh, N.; Schnürch, M.; Mihovilovic, M. D. *Org. Lett.* **2012**, *14*, 3792–3795.
- (324) Kumar, N. Y. P.; Jeyachandran, R.; Ackermann, L. *J. Org. Chem.* **2013**, *78*, 4145–4152.
- (325) Pan, S.; Endo, K.; Shibata, T. *Org. Lett.* **2011**, *13*, 4692–4695.
- (326) Spangler, J. E.; Kobayashi, Y.; Verma, P.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 11876–11879.
- (327) Jain, P.; Verma, P.; Xia, G.; Yu, J.-Q. *Nat. Chem.* **2017**, *9*, 140–144.
- (328) Xu, Y.; Dong, G. *Chem. Sci.* **2018**, *9*, 1424–1432.
- (329) Huang, Z.; Wang, C.; Dong, G. *Angew. Chem. Int. Ed.* **2016**, *55*, 5299–5303.
- (330) Topczewski, J. J.; Cabrera, P. J.; Saper, N. I.; Sanford, M. S. *Nature* **2016**, *531*, 220–224.
- (331) Cabrera, P. J.; Lee, M.; Sanford, M. S. *J. Am. Chem. Soc.* **2018**, *140*, 5599–5606.
- (332) Xu, Y.; Young, M. C.; Wang, C.; Magness, D. M.; Dong, G. *Angew. Chem. Int. Ed.* **2016**, *55*, 9084–9087.
- (333) Liu, Y.; Ge, H. *Nat. Chem.* **2017**, *9*, 26–32.
- (334) Wu, Y.; Chen, Y.-Q.; Liu, T.; Eastgate, M. D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 14554–14557.
- (335) Yada, A.; Liao, W.; Sato, Y.; Murakami, M. *Angew. Chem. Int. Ed.* **2016**, *56*, 1073–1076.
- (336) Rousseaux, S.; Gorelsky, S. I.; Chung, B. K. W.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 10692–10705.
- (337) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. *Nature* **2014**, *510*, 129–133.
- (338) Fuchita, Y.; Yoshinaga, K.; Hanaki, T.; Kawano, H.; Kinoshita-Nagaoka, J. *J. Organomet. Chem.* **1999**, *580*, 273–281.
- (339) Dunina, V. V.; Kuz'mina, L. G.; Kazakova, M. Y.; Gorunova, O. N.; Grishin, Y. K.; Kazakova, E. I. *Eur. J. Inorg. Chem.* **1999**, *1999*, 1029–1039.
- (340) Smalley, A. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 10632–10641.
- (341) Smalley, A. P.; Cuthbertson, J. D.; Gaunt, M. J. *J. Am. Chem. Soc.* **2017**, *139*, 1412–1415.
- (342) He, C.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 15840–15844.
- (343) He, C.; Gaunt, M. J. *Chem. Sci.* **2017**, *8*, 3586–3592.
- (344) Nappi, M.; He, C.; Whitehurst, W. G.; Chapell, B. G. N.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2018**, *57*, 3178–3182.
- (345) Calleja, J.; Pla, D.; Gorman, T. W.; Domingo, V.; Haffemayer, B.; Gaunt, M. J. *Nat. Chem.* **2015**, *7*, 1009–1016.
- (346) Chen, K.; Wang, D.; Li, Z.-W.; Liu, Z.; Pan, F.; Zhang, Y.-F.; Shi, Z.-J. *Org. Chem. Front.*

- 2017**, *4*, 2097–2101.
- (347) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2944.
- (348) Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274–7276.
- (349) Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11707–11711.
- (350) Jiang, C.; Covell, D. J.; Stepan, A. F.; Plummer, M. S.; White, M. C. *Org. Lett.* **2012**, *14*, 1386–1389.
- (351) Wu, L.; Qiu, S.; Liu, G. *Org. Lett.* **2009**, *11*, 2707–2710.
- (352) Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 3316–3318.
- (353) Reed, S. A.; Mazzotti, A. R.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11701–11706.
- (354) Pattillo, C. C.; Strambeanu, I. I.; Calleja, P.; Vermeulen, N. A.; Mizuno, T.; White, M. C. *J. Am. Chem. Soc.* **2016**, *138*, 1265–1272.
- (355) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898–6926.
- (356) Margrey, K. A.; Nicewicz, D. A. *Acc. Chem. Res.* **2016**, *49*, 1997–2006.
- (357) McManus, J. B.; Onuska, N. P. R.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2018**, *140*, 9056–9060.
- (358) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075–10166.
- (359) Campagna, S.; Puntoriero, F.; Nastasi, F.; Bergamini, G.; Balzani, V. *Top. Curr. Chem.* **2007**, *280*, 117–214.
- (360) Flamigni, L.; Barbieri, A.; Sabatini, C.; Ventura, B.; Barigelletti, F. *Top. Curr. Chem.* **2007**, *281*, 143–203.
- (361) Juris, A.; Balzani, V.; Barigelletti, F.; Campagna, S.; Belser, P.; von Zelewsky, A. *Coord. Chem. Rev.* **1988**, *84*, 85–277.
- (362) Arias-Rotondo, D. M.; McCusker, J. K. *Chem. Soc. Rev.* **2016**, *45*, 5803–5820.
- (363) Bock, C. R.; Connor, J. A.; Gutierrez, A. R.; Meyer, T. J.; Whitten, D. G.; Sullivan, B. P.; Nagle, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4815–4824.
- (364) Smith, J. R. L.; Masheder, D. *J. Chem. Soc., Perkin Trans. 2* **1976**, 47–51.
- (365) Hu, J.; Wang, J.; Nguyen, T. H.; Zheng, N. *Beilstein J. Org. Chem.* **2013**, *9*, 1977–2001.
- (366) Nakajima, K.; Miyake, Y.; Nishibayashi, Y. *Acc. Chem. Res.* **2016**, *49*, 1946–1956.
- (367) Beatty, J. W.; Stephenson, C. R. J. *Acc. Chem. Res.* **2015**, *48*, 1474–1484.
- (368) Schmittel, M.; Burghart, A. *Angew. Chem. Int. Ed.* **2003**, *36*, 2550–2589.
- (369) Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464–1465.
- (370) Rueping, M.; Zhu, S.; Koenigs, R. M. *Chem. Commun.* **2011**, 47, 12709–12711.
- (371) Zhao, G.; Yang, C.; Guo, L.; Sun, H.; Chen, C.; Xia, W. *Chem. Commun.* **2012**, 48, 2337–2339.

- (372) Rueping, M.; Zhu, S.; Koenigs, R. M. *Chem. Commun.* **2011**, 47, 8679–8681.
- (373) Rueping, M.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C.; Leonori, D.; Vila, C. *Chem. Eur. J.* **2012**, 18, 5170–5174.
- (374) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2012**, 14, 94–97.
- (375) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2012**, 134, 8094–8097.
- (376) Bergonzini, G.; Schindler, C. S.; Wallentin, C.-J.; Jacobsen, E. N.; Stephenson, C. R. J. *Chem. Sci.* **2014**, 5, 112–116.
- (377) Renaud, P.; Giraud, L. *Synthesis* **1996**, 1996, 913–926.
- (378) Kohls, P.; Jadhav, D.; Pandey, G.; Reiser, O. *Org. Lett.* **2012**, 14, 672–675.
- (379) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2012**, 134, 3338–3341.
- (380) Dai, X.; Cheng, D.; Guan, B.; Mao, W.; Xu, X.; Li, X. *J. Org. Chem.* **2014**, 79, 7212–7219.
- (381) Ruiz Espelt, L.; Wiensch, E. M.; Yoon, T. P. *J. Org. Chem.* **2013**, 78, 4107–4114.
- (382) Lewis, F. D.; Ho, T.-I. *J. Am. Chem. Soc.* **1980**, 102, 1751–1752.
- (383) Dai, X.; Mao, R.; Guan, B.; Xu, X.; Li, X. *RSC Adv.* **2015**, 5, 55290–55294.
- (384) Hepburn, H. B.; Melchiorre, P. *Chem. Commun.* **2016**, 52, 3520–3523.
- (385) Ju, X.; Li, D.; Li, W.; Yu, W.; Bian, F. *Adv. Synth. Catal.* **2012**, 354, 3561–3567.
- (386) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature* **2016**, 532, 218–222.
- (387) Miyake, Y.; Ashida, Y.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* **2012**, 48, 6966–6968.
- (388) Ruiz Espelt, L.; McPherson, I. S.; Wiensch, E. M.; Yoon, T. P. *J. Am. Chem. Soc.* **2015**, 137, 2452–2455.
- (389) Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, 136, 10886–10889.
- (390) Miyazawa, K.; Koike, T.; Akita, M. *Adv. Synth. Catal.* **2014**, 356, 2749–2755.
- (391) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *Chem. Eur. J.* **2012**, 18, 16473–16477.
- (392) Zhou, H.; Lu, P.; Gu, X.; Li, P. *Org. Lett.* **2013**, 15, 5646–5649.
- (393) Uraguchi, D.; Kinoshita, N.; Kizu, T.; Ooi, T. *J. Am. Chem. Soc.* **2015**, 137, 13768–13771.
- (394) Wang, C.; Qin, J.; Shen, X.; Riedel, R.; Harms, K.; Meggers, E. *Angew. Chem. Int. Ed.* **2015**, 55, 685–688.
- (395) McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, 334, 1114–1117.
- (396) Prier, C. K.; MacMillan, D. W. C. *Chem. Sci.* **2014**, 5, 4173–4178.
- (397) Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, 136, 5257–5260.
- (398) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, 345, 437–440.
- (399) Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**,



- 138, 1832–1835.
- (400) El Khatib, M.; Serafim, R. A. M.; Molander, G. A. *Angew. Chem. Int. Ed.* **2015**, *55*, 254–258.
- (401) Thullen, S. M.; Rovis, T. *J. Am. Chem. Soc.* **2017**, *139*, 15504–15508.
- (402) Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. *Science* **2012**, *338*, 647–651.
- (403) Bissember, A. C.; Lundgren, R. J.; Creutz, S. E.; Peters, J. C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 5129–5133.
- (404) Do, H.-Q.; Bachman, S.; Bissember, A. C.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 2162–2167.
- (405) Kainz, Q. M.; Matier, C. D.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. *Science* **2016**, *351*, 681–684.
- (406) Ahn, J. M.; Ratani, T. S.; Hannoun, K. I.; Fu, G. C.; Peters, J. C. *J. Am. Chem. Soc.* **2017**, *139*, 12716–12723.
- (407) Matier, C. D.; Schwaben, J.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2017**, *139*, 17707–17710.
- (408) Mao, R.; Frey, A.; Balon, J.; Hu, X. *Nat. Catal.* **2018**, *1*, 120–126.
- (409) Liang, Y.; Zhang, X.; MacMillan, D. W. C. *Nature* **2018**, *559*, 83–88.
- (410) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. *Chem. Soc. Rev.* **2016**, *45*, 546–576.
- (411) Duncton, M. A. J. *MedChemComm* **2011**, *2*, 1135.
- (412) Cowden, C. J. *Org. Lett.* **2003**, *5*, 4497–4499.
- (413) Sandip, M. *Adv. Synth. Catal.* **2018**, *360*, 1735–1753.
- (414) Cheng, W.-M.; Shang, R.; Fu, Y. *ACS Catal.* **2017**, *7*, 907–911.
- (415) Proctor, R. S. J.; Davis, H. J.; Phipps, R. J. *Science* **2018**, *360*, 419–422.
- (416) Musacchio, A. J.; Nguyen, L. Q.; Beard, G. H.; Knowles, R. R. *J. Am. Chem. Soc.* **2014**, *136*, 12217–12220.
- (417) Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; MacMillan, D. W. C. *Science* **2016**, *352*, 1304–1308.
- (418) Le, C.; Liang, Y.; Evans, R. W.; Li, X.; MacMillan, D. W. C. *Nature* **2017**, *547*, 79–83.
- (419) Mayer, J. M. *Acc. Chem. Res.* **2011**, *44*, 36–46.
- (420) Weinberg, D. R.; Gagliardi, C. J.; Hull, J. F.; Murphy, C. F.; Kent, C. A.; Westlake, B. C.; Paul, A.; Ess, D. H.; McCafferty, D. G.; Meyer, T. J. *Chem. Rev.* **2012**, *112*, 4016–4093.
- (421) Luo, Y. R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRC Press: Boca Raton, FL, 2003.
- (422) Choi, G. J.; Knowles, R. R. *J. Am. Chem. Soc.* **2015**, *137*, 9226–9229.

- (423) Miller, D. C.; Choi, G. J.; Orbe, H. S.; Knowles, R. R. *J. Am. Chem. Soc.* **2015**, *137*, 13492–13495.
- (424) Zhu, Q.; Graff, D. E.; Knowles, R. R. *J. Am. Chem. Soc.* **2018**, *140*, 741–747.
- (425) Musacchio, A. J.; Lainhart, B. C.; Zhang, X.; Naguib, S. G.; Sherwood, T. C.; Knowles, R. R. *Science* **2017**, *355*, 727–730.
- (426) Ye, J.; Kalvet, I.; Schoenebeck, F.; Rovis, T. *Nat. Chem.* **2018**.
- (427) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009.
- (428) Hajra, A.; Wei, Y.; Yoshikai, N. *Org. Lett.* **2012**, *14*, 5488–5491.
- (429) Willcox, D.; Chappell, B. G. N.; Hogg, K. F.; Calleja, J.; Smalley, A. P.; Gaunt, M. J. *Science* **2016**, *354*, 851–857.
- (430) Vargaftik, M. N.; Stromnova, T. A.; Mazo, G. Y.; Moiseev, I. I. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1982**, *31*, 1116–1120.
- (431) Stromnova, T. A.; Vargaftik, M. N.; Moiseev, I. I. *J. Organomet. Chem.* **1983**, *252*, 113–120.
- (432) Behn, A.; Head-Gordon, M.; Bell, A. T. *Organometallics* **2010**, *29*, 1144–1149.
- (433) Tsukano, C.; Okuno, M.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 2763–2766.
- (434) Dailier, D.; Rocaboy, R.; Baudoin, O. *Angew. Chem. Int. Ed.* **2017**, *56*, 7218–7222.
- (435) Liu, Y. J.; Xu, H.; Kong, W. J.; Shang, M.; Dai, H. X.; Yu, J. Q. *Nature* **2014**, *515*, 389–393.
- (436) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750–6755.
- (437) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242–3272.
- (438) Morin, R. B.; Gorman, R. *Chemistry and Biology of  $\beta$ -Lactam Antibiotics*; Academic Press UK: London, 1982.
- (439) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Curr. Opin. Drug Discov. Devel.* **2010**, *13*, 685–697.
- (440) Kudo, F.; Miyanaga, A.; Eguchi, T. *Nat. Prod. Rep.* **2014**, *31*, 1056–1073.
- (441) Kiss, L.; Fülöp, F. *Chem. Rev.* **2014**, *114*, 1116–1169.
- (442) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402–5422.
- (443) Wu, X.; Neumann, H.; Beller, M. *ChemSusChem* **2013**, *6*, 229–241.
- (444) Baudoin, O.; Herrbach, A.; Guéritte, F. *Angew. Chem. Int. Ed.* **2003**, *42*, 5736–5740.
- (445) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570–14571.
- (446) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266–3267.
- (447) Xie, P.; Xie, Y.; Qian, B.; Zhou, H.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2012**, *134*, 9902–9905.
- (448) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759–1762.

- (449) Liu, H.; Laurenczy, G.; Yan, N.; Dyson, P. J. *Chem. Commun.* **2014**, 50, 341–343.
- (450) Anas, S.; Cordi, A.; Kagan, H. B. *Chem. Commun.* **2011**, 47, 11483–11485.
- (451) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, 41, 1461–1473.
- (452) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, 47, 6338–6361.
- (453) Hartwig, J. F. *Inorg. Chem.* **2007**, 46, 1936–1947.
- (454) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, 120, 7369–7370.
- (455) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, 118, 7215–7216.
- (456) Mole, L.; Spencer, J. L.; Carr, N.; Orpen, A. G. *Organometallics* **1991**, 10, 49–52.
- (457) Marcone, J. E.; Moloy, K. G. *J. Am. Chem. Soc.* **1998**, 120, 8527–8528.
- (458) Brown, J. M.; Guiry, P. J. *Inorganica Chim. Acta* **1994**, 220, 249–259.
- (459) Kubota, A.; Emmert, M. H.; Sanford, M. S. *Org. Lett.* **2012**, 14, 1760–1763.
- (460) Davis, F. A.; Song, M. *Org. Lett.* **2007**, 9, 2413–2416.
- (461) Dai, M.; Wang, C.; Dong, G.; Xiang, J.; Luo, T.; Liang, B.; Chen, J.; Yang, Z. *European J. Org. Chem.* **2003**, 2003, 4346–4348.
- (462) van Leeuwen, P. W. N. M.; Kamer, P. C. J. *Catal. Sci. Technol.* **2018**, 8, 26–113.
- (463) Jiménez-Rodríguez, C.; Roca, F. X.; Bo, C.; Benet-Buchholz, J.; Escudero-Adán, E. C.; Freixa, Z.; van Leeuwen, P. W. N. M. *Dalt. Trans.* **2006**, 268–278.
- (464) Freixa, Z.; Beentjes, M. S.; Batema, G. D.; Dieleman, C. B.; Van Strijdonck, G. P. F.; Reek, J. N. H.; Kamer, P. C. J.; Fraanje, J.; Goubitz, K.; Van Leeuwen, P. W. N. M. *Angew. Chem. Int. Ed.* **2003**, 42, 1284–1287.
- (465) Klingensmith, L. M.; Strieter, E. R.; Barder, T. E.; Buchwald, S. L. *Organometallics* **2006**, 25, 82–91.
- (466) Sergeev, A. G.; Artamkina, G. A.; Beletskaya, I. P. *Russ. J. Org. Chem.* **2003**, 39, 1741–1752.
- (467) Ji, Y.; Plata, R. E.; Regens, C. S.; Hay, M.; Schmidt, M.; Razler, T.; Qiu, Y.; Geng, P.; Hsiao, Y.; Rosner, T.; Eastgate, M. D.; Blackmond, D. G. *J. Am. Chem. Soc.* **2015**, 137, 13272–13281.
- (468) Grushin, V. V. *Chem. Rev.* **2004**, 104, 1629–1662.
- (469) Ruch, A. A.; Handa, S.; Kong, F.; Nesterov, V. N.; Pahls, D. R.; Cundari, T. R.; Slaughter, L. M. *Org. Biomol. Chem.* **2016**, 14, 8123–8140.
- (470) Adams, G. M.; Weller, A. S. *Coord. Chem. Rev.* **2018**, 355, 150–172.
- (471) Denmark, S. E.; Smith, R. C.; Tymonko, S. A. *Tetrahedron* **2007**, 63, 5730–5738.
- (472) Tereniak, S. J.; Landis, C. R.; Stahl, S. S. *ACS Catal.* **2018**, 8, 3708–3714.
- (473) Anand, M.; Sunoj, R. B.; Schaefer, H. F. *J. Am. Chem. Soc.* **2014**, 136, 5535–5538.
- (474) Anand, M.; Sunoj, R. B.; Schaefer, H. F. *ACS Catal.* **2016**, 6, 696–708.

- (475) Sköld, C.; Kleimark, J.; Trejos, A.; Odell, L. R.; Nilsson, L. S. O.; Norrby, P.; Larhed, M. *Chem. Eur. J.* **2012**, *18*, 4714–4722.
- (476) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation - Direct Synthesis of Carbonyl Compounds*; Springer US, 1991.
- (477) Nahra, F.; Liron, F.; Prestat, G.; Mealli, C.; Messaoudi, A.; Poli, G. *Chem. Eur. J.* **2009**, *15*, 11078–11082.
- (478) Odell, L. R.; Russo, F.; Larhed, M. *Synlett* **2012**, *23*, 685–698.
- (479) Friis, S. D.; Lindhardt, A. T.; Skrydstrup, T. *Acc. Chem. Res.* **2016**, *49*, 594–605.
- (480) Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J. H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183–190.
- (481) Lednicer, D. *The Organic Chemistry of Drug Synthesis*, Volume 7.; Wiley: Hoboken: NJ, 2008.
- (482) Lazareva, A.; Daugulis, O. *Org. Lett.* **2006**, *8*, 5211–5213.
- (483) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666–7673.
- (484) Miura, M.; Feng, C.-G.; Ma, S.; Yu, J.-Q. *Org. Lett.* **2013**, *15*, 5258–5261.
- (485) Wang, P.; Farmer, M. E.; Yu, J. *Angew. Chem. Int. Ed.* **2017**, *56*, 5125–5129.
- (486) Rodríguez, A.; Albert, J.; Ariza, X.; Garcia, J.; Granell, J.; Farràs, J.; La Mela, A.; Nicolás, E. *J. Org. Chem.* **2014**, *79*, 9578–9585.
- (487) Tan, P. W.; Haughey, M.; Dixon, D. J. *Chem. Commun.* **2015**, *51*, 4406–4409.
- (488) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342–14343.
- (489) Orito, K.; Miyazawa, M.; Nakamura, T.; Horibata, A.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Yamazaki, T.; Tokuda, M. *J. Org. Chem.* **2006**, *71*, 5951–5958.
- (490) Li, H.; Cai, G.-X.; Shi, Z.-J. *Dalt. Trans.* **2010**, *39*, 10442–10446.
- (491) Lopez, B.; Rodriguez, A.; Santos, D.; Albert, J.; Ariza, X.; Garcia, J.; Granell, J. *Chem. Commun.* **2011**, *47*, 1054–1056.
- (492) Albert, J.; Ariza, X.; Calvet, T.; Font-Bardía, M.; Garcia, J.; Granell, J.; Lamela, A.; López, B.; Martinez, M.; Ortega, L.; Rodriguez, J.; Santos, D. *Organometallics* **2013**, *32*, 649–659.
- (493) Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403–424.
- (494) Chen, X.; Engle, K. M.; Wang, D.; Yu, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115.
- (495) Berthelot, M.; Gal, J. F.; Laurence, C.; Maria, P. C. *J. Chim. Phys. Phys.-Chim. Biol.* **1984**, *81*, 327–331.
- (496) Murahashi, S.-I.; Takaya, H. *Acc. Chem. Res.* **2000**, *33*, 225–233.
- (497) Keyworth, D. *J. Org. Chem.* **1959**, *24*, 1355.

- (498) Hwang, J. Y.; Kawasuji, T.; Lowes, D. J.; Clark, J. A.; Connelly, M. C.; Zhu, F.; Guiguemde, W. A.; Sigal, M. S.; Wilson, E. B.; DeRisi, J. L.; Guy, R. K. *J. Med. Chem.* **2011**, *54*, 7084–7093.
- (499) Zheng, J.; Yu, T.; Truhlar, D. G. *Phys. Chem. Chem. Phys.* **2011**, *13*, 19318–19324.
- (500) Beggs, W. H. Hahn, F. E., Ed.; *Mechanism of Action of Antibacterial Agents*, Springer Berlin Heidelberg: Berlin, Heidelberg, 1979; pp 43–66.
- (501) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437–4492.
- (502) Williams, R. M.; Lee, B. H.; Miller, M. M.; Anderson, O. P. *J. Am. Chem. Soc.* **1989**, *111*, 1073–1081.
- (503) Burkard, S.; Borschberg, H. *Helv. Chim. Acta* **1991**, *74*, 275–289.
- (504) Miknis, G. F.; Williams, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 536–547.
- (505) Snider, B. B.; Busuyek, M. V. *Tetrahedron* **2001**, *57*, 3301–3307.
- (506) Han, S.-J.; Fernando de Melo, G.; Stoltz, B. M. *Tetrahedron Lett.* **2014**, *55*, 6467–6469.
- (507) Jones, W. D. *Inorg. Chem.* **2005**, *44*, 4475–4484.
- (508) Clayden, J.; Donnard, M.; Lefranc, J.; Tetlow, D. J. *Chem. Commun.* **2011**, *47*, 4624–4639.
- (509) Hager, A.; Vrielink, N.; Hager, D.; Lefranc, J.; Trauner, D. *Nat. Prod. Rep.* **2016**, *33*, 491–522.
- (510) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83–134.
- (511) Seeman, J. I. *J. Chem. Educ.* **1986**, *63*, 42.
- (512) Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1987**, *109*, 5935–5943.
- (513) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735–1766.
- (514) Kapoor, M.; Liu, D.; Young, M. C. *J. Am. Chem. Soc.* **2018**, *140*, 6818–6822.
- (515) Lawrence, S. A. *Amines: Synthesis, Properties, and Applications*, Cambridge.; Cambridge University, 2006.
- (516) Wang, D.-H.; Hao, X.-S.; Wu, D.-F.; Yu, J.-Q. *Org. Lett.* **2006**, *8*, 3387–3390.
- (517) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312–15313.
- (518) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810–11811.
- (519) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672–3673.
- (520) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648–5649.
- (521) Dragojlovic, V. *ChemTexts* **2015**, *1*, 14.
- (522) Wiberg, K. B.; Furtek, B. L.; Olli, L. K. *J. Am. Chem. Soc.* **1979**, *101*, 7675–7679.
- (523) Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.;

- Polonchuk, L.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 7736–7739.
- (524) Carreira, E. M.; Fessard, T. C. *Chem. Rev.* **2014**, *114*, 8257–8322.
- (525) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845–5859.
- (526) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529–2591.
- (527) Beck, E. M.; Gaunt, M. J. Yu, J.-Q., Shi, Z., Eds.; Springer Berlin Heidelberg: Berlin, Heidelberg, 2010; pp 85–121.
- (528) DiPietro, D.; Borzilleri, R. M.; Weinreb, S. M. *J. Org. Chem.* **1994**, *59*, 5856–5857.
- (529) Nelsen, S. F.; Ippoliti, J. T. *J. Am. Chem. Soc.* **1986**, *108*, 4879–4881.
- (530) Lee, K. N.; Ngai, M.-Y. *Chem. Commun.* **2017**, *53*, 13093–13112.
- (531) Kunai, A.; Harada, J.; Nishihara, M.; Yanagi, Y.; Sasaki, K. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2442–2446.
- (532) Suga, S.; Suzuki, S.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 30–31.
- (533) Martin, S. F.; Yang, C.-P.; Laswell, W. L.; Rüeger, H. *Tetrahedron Lett.* **1988**, *29*, 6685–6687.
- (534) Szostak, M.; Fazakerley, N. J.; Parmar, D.; Procter, D. J. *Chem. Rev.* **2014**, *114*, 5959–6039.
- (535) Zheng, X.; He, J.; Li, H.-H.; Wang, A.; Dai, X.-J.; Wang, A.-E.; Huang, P.-Q. *Angew. Chem. Int. Ed.* **2015**, *54*, 13739–13742.
- (536) Heinz, C.; Lutz, J. P.; Simmons, E. M.; Miller, M. M.; Ewing, W. R.; Doyle, A. G. *J. Am. Chem. Soc.* **2018**, *140*, 2292–2300.
- (537) Mariano, P. S. *Tetrahedron* **1983**, *39*, 3845–3879.
- (538) Mariano, P. S. *Acc. Chem. Res.* **1983**, *16*, 130–137.
- (539) Stavinocha, J. L.; Mariano, P. S. *J. Am. Chem. Soc.* **1981**, *103*, 3136–3148.
- (540) Mariano, P. S.; Stavinocha, J.; Bay, E. *Tetrahedron* **1981**, *37*, 3385–3395.
- (541) Dieter, R.; Albert, W. *Isr. J. Chem.* **1970**, *8*, 259–271.
- (542) Cho, I. S.; Tu, C. L.; Mariano, P. S. *J. Am. Chem. Soc.* **1990**, *112*, 3594–3607.
- (543) Borg, R. M.; Heuckeroth, R. O.; Lan, A. J.; Quillen, S. L.; Mariano, P. S. *J. Am. Chem. Soc.* **1987**, *109*, 2728–2737.
- (544) Lan, A. J. Y.; Heuckeroth, R. O.; Mariano, P. S. *J. Am. Chem. Soc.* **1987**, *109*, 2738–2745.
- (545) Cho, I. S.; Mariano, P. S. *J. Org. Chem.* **1988**, *53*, 1590–1592.
- (546) Stavinocha, J. L.; Leone-Bay, A.; Swanson, R.; Bracken, C.; Mariano, P. S. *J. Am. Chem. Soc.* **1981**, *103*, 3148–3160.
- (547) Tu, C.-L.; Mariano, P. S. *J. Am. Chem. Soc.* **1987**, *109*, 5287–5288.
- (548) Ohga, K.; Yoon, U. C.; Mariano, P. S. *J. Org. Chem.* **1984**, *49*, 213–219.
- (549) Lan, A. J. Y.; Quillen, S. L.; Heuckeroth, R. O.; Mariano, P. S. *J. Am. Chem. Soc.* **1984**, *106*,

- 6439–6440.
- (550) Roubelakis, M. M.; Vougioukalakis, G. C.; Nye, L. C.; Drewello, T.; Orfanopoulos, M. *Tetrahedron* **2010**, *66*, 9363–9369.
- (551) Holý, A.; Krupička, J.; Arnold, Z. *Collect. Czech. Chem. Commun.* **1965**, *30*, 4127–4142.
- (552) Andrieux, C. P.; Savéant, J. M. *J. Electroanal. Chem.* **1970**, *26*, 223–235.
- (553) Andrieux, C. P.; Saveant, J. M. *J. Electroanal. Chem.* **1971**, *33*, 453–461.
- (554) Roth, H. G.; Romero, N. A.; Nicewicz, D. A. *Synlett* **2016**, *27*, 714–723.
- (555) Hager, D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 16986–16989.
- (556) Jeffrey, J. L.; Petronijević, F. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 8404–8407.
- (557) Nakajima, M.; Fava, E.; Loescher, S.; Jiang, Z.; Rueping, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 8828–8832.
- (558) Fava, E.; Millet, A.; Nakajima, M.; Loescher, S.; Rueping, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 6776–6779.
- (559) Qi, L.; Chen, Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 13312–13315.
- (560) de Arriba, A. L.; Urbitsch, F.; Dixon, D. J. *Chem. Commun.* **2016**, *52*, 14434–14437.
- (561) Lee, K. N.; Lei, Z.; Ngai, M.-Y. *J. Am. Chem. Soc.* **2017**, *139*, 5003–5006.
- (562) Guo, X.; Wenger, O. S. *Angew. Chem. Int. Ed.* **2017**, *57*, 2469–2473.
- (563) Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1982**, *104*, 1430–1432.
- (564) Keck, G. E.; Enholm, E. J. *Tetrahedron Lett.* **1985**, *26*, 3311–3314.
- (565) Beckwith, A. L. J.; Boate, D. R. *Tetrahedron Lett.* **1985**, *26*, 1761–1764.
- (566) Arya, P.; Wayner, D. D. M. *Tetrahedron Lett.* **1991**, *32*, 6265–6268.
- (567) Padwa, A.; Nimmesgern, H.; Wong, G. S. K. *J. Org. Chem.* **1985**, *50*, 5620–5627.
- (568) Aurrecoechea, J. M.; Fernández-Acebes, A. *Synlett* **1996**, *1996*, 39–42.
- (569) Katritzky, A. R.; Feng, D.; Qi, M.; Aurrecoechea, J. M.; Suero, R.; Aurrekoetxea, N. *J. Org. Chem.* **1999**, *64*, 3335–3338.
- (570) P. Roberts, B. *Chem. Soc. Rev.* **1999**, *28*, 25–35.
- (571) Mayol-Llinàs, J.; Farnaby, W.; Nelson, A. *Chem. Commun.* **2017**, *53*, 12345–12348.
- (572) Lahmy, V.; Long, R.; Morin, D.; Villard, V.; Maurice, T. *Front. Cell. Neurosci.* **2015**, *8*, 463.
- (573) Zhao, Y.; Aguilar, A.; Bernard, D.; Wang, S. *J. Med. Chem.* **2015**, *58*, 1038–1052.
- (574) Marciano, D. P.; Chang, M. R.; Corzo, C. A.; Goswami, D.; Lam, V. Q.; Pascal, B. D.; Griffin, P. R. *Cell Metab.* **2014**, *19*, 193–208.
- (575) Beckwith, A. L. J. *Chem. Soc. Rev.* **1993**, *22*, 143–151.
- (576) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959–974.

- (577) Aurrecochea, J. M.; López, B.; Fernández, A.; Arrieta, A.; Cossío, F. P. *J. Org. Chem.* **1997**, *62*, 1125–1135.
- (578) Shvydkiv, O.; Gallagher, S.; Nolan, K.; Oelgemöller, M. *Org. Lett.* **2010**, *12*, 5170–5173.
- (579) Douglas, J. J.; Cole, K. P.; Stephenson, C. R. J. *J. Org. Chem.* **2014**, *79*, 11631–11643.
- (580) Le, C. “Chip”; Wismer, M. K.; Shi, Z.-C.; Zhang, R.; Conway, D. V.; Li, G.; Vachal, P.; Davies, I. W.; MacMillan, D. W. C. *ACS Cent. Sci.* **2017**, *3*, 647–653.
- (581) Hofbeck, T.; Yersin, H. *Inorg. Chem.* **2010**, *49*, 9290–9299.
- (582) Cordes, E. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1962**, *84*, 832–837.
- (583) Capacci, A. G.; Malinowski, J. T.; McAlpine, N. J.; Kuhne, J.; MacMillan, D. W. C. *Nat. Chem.* **2017**, *9*, 1073.
- (584) Lakhdar, S.; Mayr, H. *Chem. Commun.* **2011**, *47*, 1866–1868.
- (585) In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Padwa, A., Bellus, D., Eds.; Science of Synthesis; Georg Thieme Verlag: Stuttgart, 2005; Vol. 27.
- (586) *CRC Handbook of Chemistry and Physics*, 99th ed.; Rumble, J. R., Ed.; CRC Press/Taylor & Francis: Boca Raton, FL., 2018.
- (587) Kiani, A.; Akhlaghinia, B.; Rouhi-Saadabad, H.; Bakavoli, M. *J. Sulfur Chem.* **2014**, *35*, 119–127.
- (588) Bartosz, G.; Jacek, M. *Eur. J. Org. Chem.* **2015**, *2015*, 5075–5078.
- (589) Miller, F. M. *J. Am. Chem. Soc.* **1953**, *75*, 4849–4850.
- (590) Sánchez, D.; Bastida, D.; Burés, J.; Isart, C.; Pineda, O.; Vilarrasa, J. *Org. Lett.* **2012**, *14*, 536–539.
- (591) Pirnot, M. T.; Rankic, D. A.; Martin, D. B. C.; MacMillan, D. W. C. *Science* **2013**, *339*, 1593–1596.
- (592) Wroblewski, M. L.; Reichard, G. A.; Paliwal, S.; Shah, S.; Tsui, H.-C.; Duffy, R. A.; Lachowicz, J. E.; Morgan, C. A.; Varty, G. B.; Shih, N.-Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3859–3863.
- (593) Nawrat, C. C.; Jamison, C. R.; Slutskyy, Y.; MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **2015**, *137*, 11270–11273.
- (594) Allgäuer, D. S.; Jangra, H.; Asahara, H.; Li, Z.; Chen, Q.; Zipse, H.; Ofial, A. R.; Mayr, H. *J. Am. Chem. Soc.* **2017**, *139*, 13318–13329.
- (595) Zhang, P.; Xiao, T.; Xiong, S.; Dong, X.; Zhou, L. *Org. Lett.* **2014**, *16*, 3264–3267.
- (596) Wille, U. *Chem. Rev.* **2013**, *113*, 813–853.
- (597) Giese, B.; Lachhein, S. *Angew. Chem. Int. Ed.* **1982**, *21*, 768–775.
- (598) Gnás, Y.; Glorius, F. *Synthesis* **2006**, *2006*, 1899–1930.



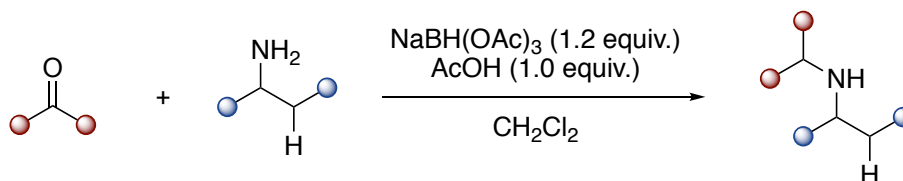
- (599) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743.
- (600) Tsantrizos, Y. S. *Acc. Chem. Res.* **2008**, *41*, 1252–1263.
- (601) Fosgerau, K.; Hoffmann, T. *Drug Discov. Today* **2015**, *20*, 122–128.
- (602) Blaskovich, M. A. T. *J. Med. Chem.* **2016**, *59*, 10807–10836.
- (603) Beckwith, A. L. J.; Chai, C. L. L. *J. Chem. Soc., Chem. Commun.* **1990**, 1087–1088.
- (604) Karady, S.; Amto, J. S.; Weinstock, L. M. *Tetrahedron Lett.* **1984**, *25*, 4337–4340.
- (605) Seebach, D.; Fadel, A. *Helv. Chim. Acta* **2018**, *68*, 1243–1250.
- (606) Aycok, R. A.; Vogt, D. B.; Jui, N. T. *Chem. Sci.* **2017**, *8*, 7998–8003.
- (607) Kanzian, T.; Nigst, T. A.; Maier, A.; Pichl, S.; Mayr, H. *Eur. J. Org. Chem.* **2009**, *2009*, 6379–6385.
- (608) Silvi, M.; Verrier, C.; Rey, Y. P.; Buzzetti, L.; Melchiorre, P. *Nat. Chem.* **2017**, *9*, 868.
- (609) Shih, H.-W.; Vander Wal, M. N.; Grange, R. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 13600–13603.
- (610) Rosokha, S. V.; Kochi, J. K. *Acc. Chem. Res.* **2008**, *41*, 641–653.
- (611) Griller, D.; Lossing, F. P. *J. Am. Chem. Soc.* **1981**, *103*, 1586–1587.
- (612) Yu, P.; Lin, J.-S.; Li, L.; Zheng, S.-C.; Xiong, Y.-P.; Zhao, L.-J.; Tan, B.; Liu, X.-Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 11890–11894.
- (613) Huang, L.; Zheng, S.-C.; Tan, B.; Liu, X.-Y. *Org. Lett.* **2015**, *17*, 1589–1592.
- (614) Lonca, G. H.; Ong, D. Y.; Tran, T. M. H.; Tejo, C.; Chiba, S.; Gagosz, F. *Angew. Chem. Int. Ed.* **2017**, *56*, 11440–11444.
- (615) Wayner, D. D. M.; Dannenberg, J. J.; Griller, D. *Chem. Phys. Lett.* **1986**, *131*, 189–191.
- (616) Taraban, M. B.; Kruppa, A. I.; Polyakov, N. E.; Leshina, T. V.; Lūsis, V.; Muceniece, D.; Duburs, G. *J. Photochem. Photobiol. A Chem.* **1993**, *73*, 151–157.
- (617) Kruppa, A. I.; Taraban, M. B.; Polyakov, N. E.; Leshina, T. V.; Lūsis, V.; Muceniece, D.; Duburs, G. *J. Photochem. Photobiol. A Chem.* **1993**, *73*, 159–163.
- (618) Jin, M.-Z.; Yang, L.; Wu, L.-M.; Liu, Y.-C.; Liu, Z.-L. *Chem. Commun.* **1998**, 2451–2452.
- (619) Zhang, J.; Jin, M. Z.; Zhang, W.; Yang, L.; Liu, Z. L. *Tetrahedron Lett.* **2002**, *43*, 9687–9689.
- (620) Jung, J.; Kim, J.; Park, G.; You, Y.; Cho, E. J. *Adv. Synth. Catal.* **2015**, *358*, 74–80.
- (621) Huang, X.; Luo, S.; Burghaus, O.; Webster, R. D.; Harms, K.; Meggers, E. *Chem. Sci.* **2017**, *8*, 7126–7131.
- (622) Simons, F. E. R. *N. Engl. J. Med.* **2004**, *351*, 2203–2217.
- (623) Certa, H.; Blaschke, G. *Arch. Pharm.* **1990**, *323*, 744–747.
- (624) Su, T.-P.; Hayashi, T.; Maurice, T.; Buch, S.; Ruoho, A. E. *Trends Pharmacol. Sci.* **2010**, *31*, 557–566.

- (625) Hickmott, P. W. *Tetrahedron* **1982**, 38, 1975–2050.
- (626) Wood, M. E.; Bissiriou, S.; Lowe, C.; Windeatt, K. M. .
- (627) Kabalka, G. W.; Pagni, R. M.; Bridwell, P.; Walsh, E.; Hassaneen, H. M. *J. Org. Chem.* **1981**, 46, 1513–1514.
- (628) Wayner, D. D. M.; McPhee, D. J.; Griller, D. *J. Am. Chem. Soc.* **1988**, 110, 132–137.
- (629) Endo, K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, 133, 8525–8527.
- (630) Bowles, P.; Clayden, J.; Helliwell, M.; McCarthy, C.; Tomkinson, M.; Westlund, N. *J. Chem. Soc. Perkin Trans. 1* **1997**, 2607–2616.
- (631) Fan, X.; Lv, H.; Guan, Y.-H.; Zhu, H.-B.; Cui, X.-M.; Guo, K. *Chem. Commun.* **2014**, 50, 4119–4122.
- (632) Miller, D. C.; Martin, M. P.; Adhikari, S.; Brennan, A.; Endicott, J. A.; Golding, B. T.; Hardcastle, I. R.; Heptinstall, A.; Hobson, S.; Jennings, C.; Molyneux, L.; Ng, Y.; Wedge, S. R.; Noble, M. E. M.; Cano, C. *Org. Biomol. Chem.* **2018**, 16, 1843–1850.
- (633) Kitbunnadaj, R.; Zuiderveld, O. P.; Christophe, B.; Hulscher, S.; Menge, W. M. P. B.; Gelens, E.; Snip, E.; Bakker, R. A.; Celanire, S.; Gillard, M.; Talaga, P.; Timmerman, H.; Leurs, R. *J. Med. Chem.* **2004**, 47, 2414–2417.
- (634) Musonda, C. C.; Yardley, V.; Carvalho de Souza, R. C.; Ncokazi, K.; Egan, T. J.; Chibale, K. *Org. Biomol. Chem.* **2008**, 6, 4446–4451.
- (635) Takise, R.; Muto, K.; Yamaguchi, J.; Itami, K. *Angew. Chem. Int. Ed.* **2014**, 53, 6791–6794.
- (636) Braschi, I.; Cardillo, G.; Tomasini, C.; Venezia, R. *J. Org. Chem.* **1994**, 59, 7292–7298.
- (637) Karagiozov, S. K.; Abbott, F. S. *Synth. Commun.* **2004**, 34, 871–888.
- (638) Suzuki, T.; Imanashi, N.; Itahana, H.; Watanuki, S.; Miyata, K.; Ohta, M.; Nakahara, H.; Yamagiwa, Y.; Mase, T. *Chem. Pharm. Bull.* **1998**, 46, 1116–1124.
- (639) Afzal, M.; C. Walton, J. *J. Chem. Soc. Perkin Trans. 2* **1999**, 937–946.
- (640) Wentland, M. P.; Perni, R. B.; Dorff, P. H.; Rake, J. B. *J. Med. Chem.* **1988**, 31, 1694–1697.
- (641) Lacheretz, R.; Pardo, D. G.; Cossy, J. *Org. Lett.* **2009**, 11, 1245–1248.
- (642) Burkhard, J. A.; Guérot, C.; Knust, H.; Rogers-Evans, M.; Carreira, E. M. *Org. Lett.* **2010**, 12, 1944–1947.
- (643) Guino, M.; Kuok (Mimi) Hii, K. *Org. Biomol. Chem.* **2005**, 3, 3188–3193.
- (644) McCabe, P. H.; Milne, N. J.; Sim, G. A. *J. Chem. Soc. Perkin Trans. 2* **1989**, 1459–1462.
- (645) Lawson, M.; Hamze, A.; Peyrat, J.-F.; Bignon, J.; Dubois, J.; Brion, J.-D.; Alami, M. *Org. Biomol. Chem.* **2013**, 11, 3664–3673.
- (646) Fujita, K.; Yamashita, M.; Puschmann, F.; Alvarez-Falcon, M. M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, 128, 9044–9045.

- (647) Sulmon, P.; De Kimpe, N.; Schamp, N. *Tetrahedron* **1989**, 45, 2937–2955.

## Appendix I: Miscellaneous Experimental Procedures

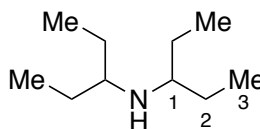
### General Procedure D for Reductive Amination



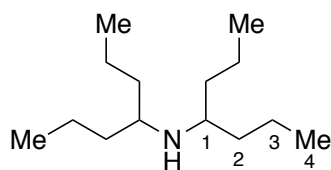
To a stirred solution of amine (50 mmol, 1.0 to 2.5 eq.), ketone/aldehyde (50 mmol, 1.0 to 2.5 eq.) and acetic acid (50 mmol, 1.0 eq.) in dichloromethane (200 mL) at 0 °C under N<sub>2</sub>, was added sodium triacetoxyborohydride (60 mmol, 1.2 eq.) portionwise over 10 minutes. The reaction mixture was allowed to warm to room temperature over 12 hours and stirred for an additional 24 to 72 hours at room temperature. After this time, the reaction mixture was quenched with 1M NaOH and was allowed to stir at room temperature for an additional 30 minutes. The mixture was then extracted with dichloromethane (3 x 100 mL) and the organics combined, washed with brine (2 x 150 mL), and dried over MgSO<sub>4</sub>. The solvent was removed *in vacuo* to give the crude amine. Further purification by kugelrohr or column chromatography afforded the corresponding amine as a liquid/oil.

#### i) Synthesis of Starting Amines for Methylene C–H Carbonylation

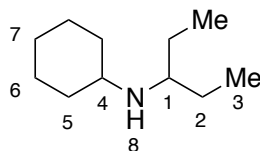
##### Di(pentan-3-yl)amine **492**



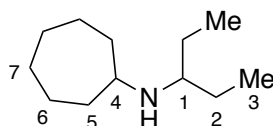
General procedure D was applied to 3-aminopentane (4.36 g, 50 mmol) and 3-pentanone (4.31 g, 50 mmol) in dichloromethane (200 mL). The mixture was left to stir at room temperature for 72 hours. Purification by kugelrohr (42 °C, 2 mbar) gave desired amine as a colourless liquid (5.60 g, 71%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2956, 2925, 2853, 1449, 1368, 1348; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 2.38 (2 H, qt,  $J$  = 6.0 Hz, H<sub>1</sub>), 1.44 – 1.32 (8 H, m, H<sub>2</sub>), 0.87 (12 H, t,  $J$  = 7.2 Hz, H<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 57.2 (C<sub>1</sub>), 26.5 (C<sub>2</sub>), 10.1 (C<sub>3</sub>);  $m/z$  HRMS found  $[M + H]^+$  158.1900, C<sub>10</sub>H<sub>24</sub>N requires 158.1903.

*Di(heptan-4-yl)amine 523a*

General procedure D was applied to 4-heptylamine (5.76 g, 50 mmol) and 4-heptanone (5.71 g, 50 mmol) in dichloromethane (200 mL). The mixture was left to stir at room temperature for 72 hours. Purification by kugelrohr (95 °C, 9 mbar) gave the desired amine as a colourless liquid (0.99 g, 9%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2956, 2928, 2872, 1465, 1378;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.50 (2 H, br s,  $\text{H}_1$ ), 1.36 (8 H, br s,  $\text{H}_2$ ), 0.92 – 0.88 (20 H, m,  $\text{H}_3$ ,  $\text{H}_4$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 54.4 ( $\text{C}_1$ ), 37.2 ( $\text{C}_2$ ), 19.0 ( $\text{C}_3$ ), 14.6 ( $\text{C}_4$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  214.2525,  $\text{C}_{14}\text{H}_{32}\text{N}$  requires 214.2529. Data consistent with literature<sup>630</sup>.

*N-(pentan-3-yl)cyclohexylamine 477*

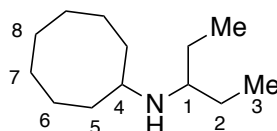
General procedure D was applied to cyclohexylamine (5.69 g, 57 mmol) and 3-pentanone (4.94 g, 57 mmol) in dichloromethane (250 mL) without acetic acid. The mixture was left to stir at room temperature for 48 hours. Purification by kugelrohr (80 °C, 3 mbar) gave the desired amine as a colourless liquid (5.40 g, 56%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2960, 2929, 2877, 1459, 1378;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.47 – 2.40 (2 H, m,  $\text{H}_1$ ,  $\text{H}_4$ ), 1.84 (2 H, dd,  $J = 2.5, 12.5$  Hz,  $\text{H}_{5a}$ ), 1.70 (2 H, dt,  $J = 3.5, 13.0$  Hz,  $\text{H}_{6a}$ ), 1.61 – 1.57 (1 H, m,  $\text{H}_{7a}$ ), 1.44 – 1.09 (6 H, m,  $\text{H}_2$ ,  $\text{H}_{6b}$ ), 1.01 (2 H, dq,  $J = 3.4, 10.9$  Hz,  $\text{H}_{5b}$ ), 0.85 (6 H, t,  $J = 7.5$  Hz,  $\text{H}_3$ ), 0.68 (1 H, br s,  $\text{H}_8$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 56.8 ( $\text{C}_1$ ), 54.0 ( $\text{C}_4$ ), 34.5 ( $\text{C}_5$ ), 26.8 ( $\text{C}_2$ ), 26.4 ( $\text{C}_7$ ), 25.5 ( $\text{C}_6$ ), 10.2 ( $\text{C}_3$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  170.1901,  $\text{C}_{11}\text{H}_{24}\text{N}$  requires 170.1903.

*N-(pentan-3-yl)cycloheptanamine 523b*

General procedure D was applied to cycloheptylamine (5.66 g, 50 mmol) and 3-pentanone (4.31 g, 50 mmol) in dichloromethane (200 mL). The mixture was left to stir at room temperature for 48 hours. Purification by kugelrohr (85 °C, 9 mbar) gave the desired amine as a colourless liquid (2.84

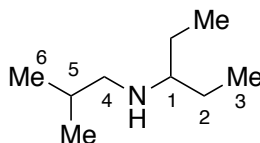
g, 32%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2958, 2921, 2853, 1459, 1379;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.67 – 2.62 (1 H, m,  $\text{H}_4$ ), 2.39 (1 H, qt,  $J = 5.9$  Hz,  $\text{H}_1$ ), 1.81 – 1.77 (2 H, m,  $\text{H}_{5a}$ ), 1.65 – 1.60 (2 H, m,  $\text{H}_{6a}$ ), 1.57 – 1.47 (4 H, m,  $\text{H}_7$ ), 1.47 – 1.30 (8 H, m,  $\text{H}_2$ ,  $\text{H}_{5b}$ ,  $\text{H}_{6b}$ ), 0.86 (6 H, t,  $J = 7.5$  Hz,  $\text{H}_3$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 57.1 ( $\text{C}_1$ ), 56.1 ( $\text{C}_4$ ), 35.6 ( $\text{C}_5$ ), 28.4 ( $\text{C}_7$ ), 26.6 ( $\text{C}_2$ ), 24.5 ( $\text{C}_6$ ), 10.1 ( $\text{C}_3$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  184.2060,  $\text{C}_{12}\text{H}_{26}\text{N}$  requires 184.2055.

*N*-(pentan-3-yl)cyclooctanamine **523c**

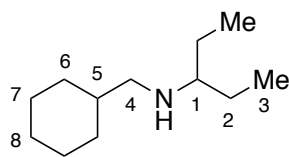


General procedure D was applied to cyclooctylamine (6.36 g, 50 mmol) and 3-pentanone (8.62 g, 100 mmol) in dichloromethane (200 mL). The mixture was left to stir at room temperature for 72 hours. Purification by kugelrohr (110 °C, 12 mbar) gave the desired amine as a colourless liquid (2.97 g, 30%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2917, 2851, 1461, 1379;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.69 (1 H, br s,  $\text{H}_4$ ), 2.38 (1 H, qt,  $J = 5.9$  Hz,  $\text{H}_1$ ), 1.72 – 1.30 (18 H, m,  $\text{H}_2$ ,  $\text{H}_5$ ,  $\text{H}_6$ ,  $\text{H}_7$ ,  $\text{H}_8$ ), 0.86 (6 H, t,  $J = 7.4$  Hz,  $\text{H}_3$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 56.9 ( $\text{C}_1$ ), 54.6 ( $\text{C}_4$ ), 33.1 ( $\text{C}_5$ ), 27.6 ( $\text{C}_7$ ), 26.6 ( $\text{C}_2$ ), 25.9 ( $\text{C}_8$ ), 24.2 ( $\text{C}_6$ ), 10.2 ( $\text{C}_3$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  198.2213,  $\text{C}_{13}\text{H}_{28}\text{N}$  requires 198.2216.

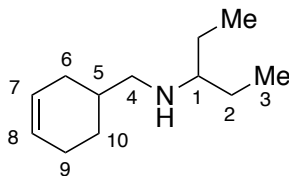
*N*-isobutylpentan-3-amine **525a**



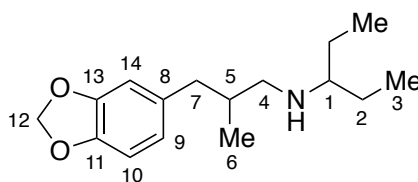
General procedure D was applied to isobutyraldehyde (1.80 g, 25 mmol) and 3-aminopentane (2.18 g, 25 mmol) in dichloromethane (100 mL). The mixture was left to stir at room temperature for 72 hours. Purification by kugelrohr (90 °C, 60 mbar) gave the desired amine as a colourless liquid (1.88 g, 53%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2957, 2925, 2872, 2802, 1461, 1380, 1364;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.36 (2 H, d,  $J = 7.0$  Hz,  $\text{H}_4$ ), 2.31 (1 H, qt,  $J = 6.0$  Hz,  $\text{H}_1$ ), 1.69 (1 H, spt,  $J = 7.0$  Hz,  $\text{H}_5$ ), 1.44 – 1.37 (4 H, m,  $\text{H}_2$ ), 0.90 (6 H, d,  $J = 6.8$  Hz,  $\text{H}_6$ ), 0.87 (6 H, t,  $J = 7.3$  Hz,  $\text{H}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 60.3 ( $\text{C}_1$ ), 55.4 ( $\text{C}_4$ ), 28.7 ( $\text{C}_5$ ), 26.1 ( $\text{C}_2$ ), 20.9 ( $\text{C}_6$ ), 10.1 ( $\text{C}_3$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  144.1743,  $\text{C}_9\text{H}_{22}\text{N}$  requires 144.1747.

*N*-(cyclohexylmethyl)pentan-3-amine **525b**

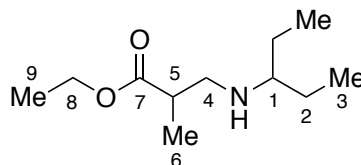
General procedure D was applied to cyclohexanemethylamine (4.98 g, 44 mmol) and 3-pentanone (5.69 g, 66 mmol) in dichloromethane (200 mL). The mixture was left to stir at room temperature for 36 hours. Purification by kugelrohr (75 °C, 10 mbar) gave the desired amine as a colourless liquid (6.87 g, 85%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2959, 2921, 2852, 1449, 1379;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.37 (2 H, d,  $J = 6.6$  Hz,  $\text{H}_4$ ), 2.29 (1 H, qt,  $J = 5.9$  Hz,  $\text{H}_1$ ), 1.75 – 1.63 (5 H, m,  $\text{H}_{6a}$ ,  $\text{H}_{7a}$ ,  $\text{H}_{8a}$ ), 1.42 – 1.36 (5 H, m,  $\text{H}_2$ ,  $\text{H}_5$ ), 1.26 – 1.13 (3 H, m,  $\text{H}_{7b}$ ,  $\text{H}_{8b}$ ), 0.92 (2 H, dt,  $J = 3.0, 12.0$  Hz,  $\text{H}_{6b}$ ), 0.85 (6 H, t,  $J = 7.5$  Hz,  $\text{H}_3$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 60.3 ( $\text{C}_1$ ), 54.0 ( $\text{C}_4$ ), 38.4 ( $\text{C}_5$ ), 31.8 ( $\text{C}_6$ ), 26.9 ( $\text{C}_8$ ), 26.2 ( $\text{C}_7$ ), 26.0 ( $\text{C}_2$ ), 10.1 ( $\text{C}_3$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  184.2055,  $\text{C}_{12}\text{H}_{26}\text{N}$  requires 184.2060.

*N*-(cyclohex-3-en-1-ylmethyl)pentan-3-amine **525c**

General procedure D was applied to cyclohex-3-enecarboxaldehyde (2.80 g, 25 mmol) and 3-aminopentane (2.18 g, 25 mmol) in dichloromethane (100 mL). The mixture was left to stir at room temperature for 72 hours. Purification by kugelrohr (128 °C, 7 mbar) gave the desired amine as a colourless liquid (3.47 g, 77%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3022, 2960, 2913, 2874, 2837, 1652, 1460, 1436, 1379;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.66 – 5.65 (2 H, m,  $\text{H}_7$ ,  $\text{H}_8$ ), 2.47 (2 H,  $d_{\text{app}}$ ,  $J = 5.0$  Hz,  $\text{H}_4$ ), 2.33 (1 H, qt,  $J = 5.9$  Hz,  $\text{H}_1$ ), 2.14 – 2.02 (3 H, m,  $\text{H}_{6a}$ ,  $\text{H}_{10}$ ), 1.81 – 1.65 (3 H, m,  $\text{H}_5$ ,  $\text{H}_{6b}$ ,  $\text{H}_{9a}$ ), 1.44 – 1.37 (4 H, m,  $\text{H}_2$ ), 1.29 – 1.19 (1 H, m,  $\text{H}_{9b}$ ), 0.87 (6 H, dt,  $J = 1.0, 7.4$  Hz,  $\text{H}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  127.3 ( $\text{C}_8$ ), 126.4 ( $\text{C}_7$ ), 60.3 ( $\text{C}_1$ ), 53.2 ( $\text{C}_4$ ), 34.4 ( $\text{C}_5$ ), 30.4 ( $\text{C}_6$ ), 27.3 ( $\text{C}_9$ ), 26.1 ( $\text{C}_{2a}$ ), 26.1 ( $\text{C}_{2b}$ ), 25.1 ( $\text{C}_{10}$ ), 10.1 ( $\text{C}_{3a}$ ), 10.1 ( $\text{C}_{3b}$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  182.1899,  $\text{C}_{12}\text{H}_{24}\text{N}$  requires 182.1903.

*N*-(2-methyl-3-(3,4-methylenedioxyphenyl)propyl)pentan-3-amine **525f**

General procedure D was applied with 2-methyl-3-(3,4-methylenedioxyphenyl)-propanal (4.81 g, 25 mmol) and 3-aminopentane (2.18 g, 25 mmol) in dichloromethane (100 mL). The mixture was left to stir at room temperature for 24 hours. Purification by flash column chromatography (gradient elution: 100% petroleum ether to 30% ethyl acetate in petroleum ether) and kugelrohr (140 °C, 0.44 mbar) gave the desired amine as a colourless liquid (4.84 g, 74%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2958, 2923, 2874, 1610, 1503, 1488, 1459, 1440, 1378, 1244;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.72 (1 H, d,  $J$  = 7.9 Hz,  $\text{H}_{10}$ ), 6.66 (1 H, d,  $J$  = 1.4 Hz,  $\text{H}_{14}$ ), 6.60 (1 H, dd,  $J$  = 1.4, 7.9 Hz,  $\text{H}_9$ ), 5.91 (2 H, s,  $\text{H}_{12}$ ), 2.67 (1 H, dd,  $J$  = 6.0 Hz, 13.4 Hz,  $\text{H}_{7a}$ ), 2.50 (1 H, dd,  $J$  = 6.0, 11.5 Hz,  $\text{H}_{4a}$ ), 2.39 (1 H, dd,  $J$  = 6.7, 11.5 Hz,  $\text{H}_{4b}$ ), 2.32 – 2.26 (2 H, m,  $\text{H}_{7b}$ ,  $\text{H}_1$ ), 1.87 – 1.77 (1 H, m,  $\text{H}_5$ ), 1.43 – 1.35 (4 H, m,  $\text{H}_2$ ), 0.89 – 0.84 (6 H, m,  $\text{H}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 147.4 ( $\text{C}_{13}$ ), 145.5 ( $\text{C}_{11}$ ), 135.0 ( $\text{C}_8$ ), 121.9 ( $\text{C}_9$ ), 109.5 ( $\text{C}_{14}$ ), 107.9 ( $\text{C}_{10}$ ), 100.7 ( $\text{C}_{12}$ ), 60.1 ( $\text{C}_1$ ), 53.1 ( $\text{C}_4$ ), 41.3 ( $\text{C}_7$ ), 35.9 ( $\text{C}_5$ ), 26.0 ( $\text{C}_{2a}$ ), 25.9 ( $\text{C}_{2b}$ ), 18.0 ( $\text{C}_6$ ), 10.0 ( $\text{C}_{3a}$ ), 9.9 ( $\text{C}_{3b}$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  264.1955,  $\text{C}_{16}\text{H}_{26}\text{O}_2\text{N}$  requires 264.1958.

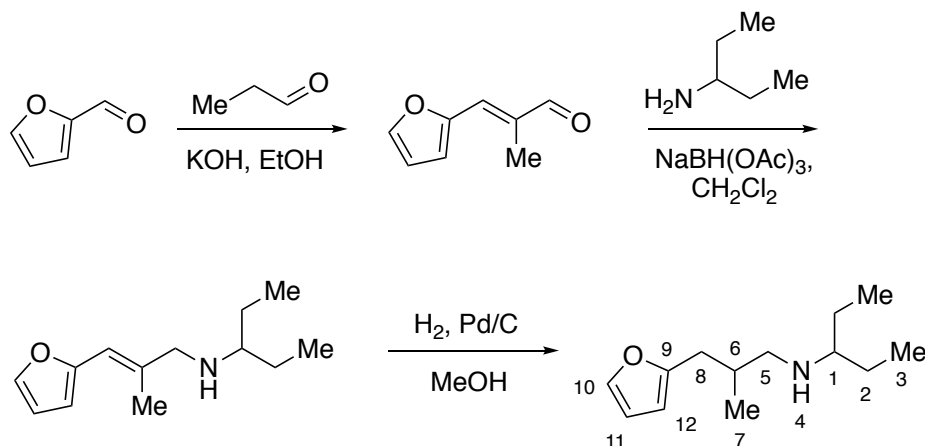
*Ethyl 2-methyl-3-(pentan-3-ylamino)propanoate* **525g**

Ethyl methacrylate (1.71 g, 15 mmol) and 3-aminopentane (2.61 g, 30 mmol) were refluxed in absolute ethanol (25 mL) for 72 hours. After such time the reaction mixture was cooled to room temperature and solvent removed *in vacuo*. The remaining oil was purified by flash column chromatography (gradient elution: 100% petroleum ether to 30% ethyl acetate in petroleum ether) to give the desired amine as a colourless liquid (0.77 g, 25%). (N.B. Subjection of the compound to high vacuum leads to decomposition at room temperature *via* a retro-Michael addition).  $R_f$  (20% ethyl acetate in petroleum ether): 0.16; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2964, 2934, 2877, 1731, 1461, 1377, 1348;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.14 (2 H, q,  $J$  = 7.2 Hz,  $\text{H}_8$ ), 2.81 (1 H, dt,  $J$  = 2.2, 9.7 Hz,  $\text{H}_{4a}$ ), 2.63 – 2.56 (2 H, m,  $\text{H}_{4b}$ ,  $\text{H}_5$ ), 2.33 (1 H, qt,  $J$  = 5.9 Hz,  $\text{H}_1$ ), 1.43 – 1.32 (4 H, m,  $\text{H}_2$ ), 1.25 (3 H, t,  $J$  = 7.3 Hz,  $\text{H}_9$ ), 1.16 (3 H, d,  $J$  = 6.8 Hz,  $\text{H}_6$ ), 0.86 (6 H, t,  $J$  = 7.5 Hz,  $\text{H}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ :



176.1 (C<sub>7</sub>), 60.3 (C<sub>8</sub>), 59.8 (C<sub>1</sub>), 50.0 (C<sub>4</sub>), 40.5 (C<sub>5</sub>), 26.0 (C<sub>2a</sub>), 25.8 (C<sub>2b</sub>), 15.4 (C<sub>6</sub>), 14.2 (C<sub>9</sub>), 9.9 (C<sub>3a</sub>), 9.8 (C<sub>3b</sub>); m/z HRMS found [M + H]<sup>+</sup> 202.1798, C<sub>11</sub>H<sub>24</sub>O<sub>2</sub>N requires 202.1802.

*N*-(3-(furan-2-yl)-2-methylpropyl)pentan-3-amine **525h**



**Step 1**

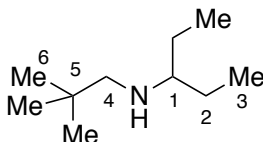
To a solution of potassium hydroxide (2.80 g, 50 mmol) in absolute ethanol (125 mL) was added furfuraldehyde (4.80 g, 50 mmol) dropwise at 0 °C. The solution was stirred at 0 °C for 15 minutes after which time propionaldehyde (5.81 g, 100 mmol) was added slowly dropwise over 15 minutes. The solution was stirred at 0 °C for 6 hours and quenched with 3M HCl (250 mL). The solution was extracted with diethyl ether (3 x 150 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. The organics were removed *in vacuo* to give (*E*)-3-(furan-2-yl)-2-methylacrylaldehyde as an orange oil (6.81 g, 100%). The product was used in the next step without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 9.50 (1 H, s), 7.62 (1 H, d, *J* = 1.6 Hz), 7.03 (1 H, d, 1.0 Hz), 6.78 (1 H, d, *J* = 3.5 Hz), 6.57 (1 H, dd, *J* = 1.7, 3.4 Hz), 2.11 (3 H, dd, *J* = 2.0 Hz). Data consistent with literature<sup>631</sup>.

**Step 2**

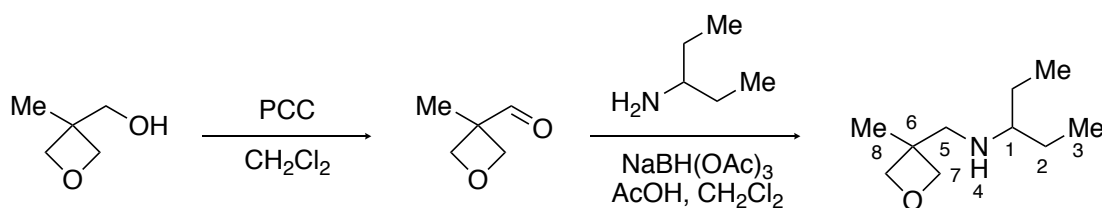
General procedure D was applied with (*E*)-3-(furan-2-yl)-2-methylacrylaldehyde (6.81 g, 50 mmol) from Step 1 and 3-aminopentane (5.05 g, 58 mmol) in dichloromethane (250 mL) without acetic acid. The mixture was left to stir at room temperature for 36 hours. The resulting (*E*)-*N*-(3-(furan-2-yl)-2-methylallyl)pentan-3-amine was obtained as a brown oil (10.37 g, 100%). The product was used in the next step without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.36 (1 H, d, *J* = 1.6 Hz), 6.39 (1 H, dd, *J* = 2.0, 3.5 Hz), 6.28 (1 H, app s), 6.23 (1 H, d, *J* = 3.3 Hz), 3.27 (2 H, s), 2.39 (1 H, qt, *J* = 6.0 Hz), 2.01 (3 H, s), 1.47 – 1.39 (4 H, m), 0.89 (6 H, t, *J* = 7.5 Hz).

**Step 3**

To a solution of (*E*)-N-(3-(furan-2-yl)-2-methylallyl)pentan-3-amine (5.18 g, 25 mmol) from Step 2 in methanol (12.5 mL) was added 10% palladium on carbon (0.25 g). The flask was sealed and purged with hydrogen (3 cycles). The mixture was stirred at room temperature for 9 hours after which time the reaction was filtered over celite and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (gradient elution: 100% petroleum ether to 30% ethyl acetate in petroleum ether) and subsequently by kugelrohr (85 °C, 0.45 mbar) to give the desired product as a colourless liquid (1.02 g, 20%).  $R_f$  (20% ethyl acetate in petroleum ether): 0.13; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2959, 2928, 2874, 1597, 1507, 1459, 1380, 1147, 1089, 1007;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.29 (1 H, dd,  $J = 0.7, 1.8$  Hz,  $\text{H}_{10}$ ), 6.27 (1 H, dd,  $J = 1.9, 3.0$  Hz,  $\text{H}_{11}$ ), 5.99 (1 H, dd,  $J = 0.7, 3.0$  Hz,  $\text{H}_{12}$ ), 2.73 (1 H, dd,  $J = 5.8, 14.8$  Hz,  $\text{H}_{8a}$ ), 2.52 – 2.38 (3 H, m,  $\text{H}_{8b}$  and  $\text{H}_5$ ), 2.32 (1 H, qt,  $J = 5.8$  Hz,  $\text{H}_1$ ), 1.99 – 1.91 (1 H, m,  $\text{H}_6$ ), 1.43 – 1.45 (4 H, m,  $\text{H}_2$ ), 1.17 (1 H, br s,  $\text{H}_4$ ), 0.93 (3 H, d,  $J = 6.7$  Hz,  $\text{H}_7$ ), 0.87 (6 H, t,  $J = 7.5$  Hz,  $\text{H}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 155.3 ( $\text{C}_9$ ), 140.9 ( $\text{C}_{10}$ ), 110.2 ( $\text{C}_{11}$ ), 106.0 ( $\text{C}_{12}$ ), 60.2 ( $\text{C}_1$ ), 52.9 ( $\text{C}_5$ ), 33.6 ( $\text{C}_6$ ), 33.4 ( $\text{C}_8$ ), 26.1 ( $\text{C}_{2a}$ ), 26.0 ( $\text{C}_{2b}$ ), 18.4 ( $\text{C}_7$ ), 10.1 ( $\text{C}_{3a}$ ), 10.0 ( $\text{C}_{3b}$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  210.1850,  $\text{C}_{13}\text{H}_{24}\text{NO}$  requires 210.1852.

*N*-neopentylpentan-3-amine **527a**

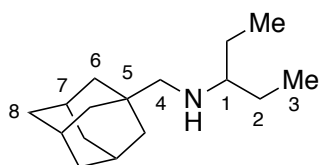
General procedure D was applied to 3-aminopentane (2.18 g, 25 mmol) and pivaldehyde (2.15 g, 25 mmol) in dichloromethane (100 mL). The mixture was left to stir at room temperature for 42 hours. Purification by kugelrohr (75 °C, 20 mbar) gave the desired amine as a colourless liquid (2.54 g, 65%). IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2954, 2874, 2809, 1462, 1362;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.29 (2 H, s,  $\text{H}_4$ ), 2.27 (1 H, qt,  $J = 6.0$  Hz,  $\text{H}_1$ ), 1.44 – 1.34 (4 H, m,  $\text{H}_2$ ), 0.90 (9 H, s,  $\text{H}_6$ ), 0.87 (6 H, t,  $J = 7.5$  Hz,  $\text{H}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 61.2 ( $\text{C}_1$ ), 59.4 ( $\text{C}_4$ ), 31.7 ( $\text{C}_5$ ), 28.0 ( $\text{C}_6$ ), 26.3 ( $\text{C}_2$ ), 10.2 ( $\text{C}_3$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  158.1899,  $\text{C}_{10}\text{H}_{24}\text{N}$  requires 158.1903.

*N*-((3-methyloxetan-3-yl)methyl)pentan-3-amine **527b****Step 1**

To a suspension of pyridinium chlorochromate (8.61 g, 40 mmol) and celite (2.5 g) in anhydrous dichloromethane (100 mL) was added a solution of (3-methyloxetan-3-yl)methanol (2.55 g, 25 mmol) in anhydrous dichloromethane (25 mL) dropwise over 30 minutes. The mixture was stirred for 5 hours at room temperature, filtered over a silica plug and washed with excess dichloromethane. The combined organics were removed carefully by rotary evaporation (30 °C, 500 mbar then 0 °C, 100 mbar) to give 3-methyloxetane-3-carboxaldehyde as a pale green liquid (1.01 g, 40%). The product was used in the next step without further purification.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.95 (1 H, s), 4.87 (2 H, d,  $J = 6.3$  Hz), 4.50 (2 H, d,  $J = 6.3$  Hz), 1.47 (3 H, s). Data consistent with literature<sup>632</sup>.

**Step 2**

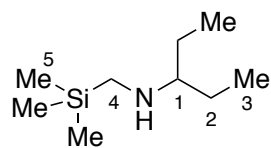
General procedure D was applied with crude 3-methyloxetane-3-carboxaldehyde from Step 1 (1.01 g, 10 mmol) and 3-aminopentane (2.18 g, 25 mmol) in dichloromethane (100 mL) without acetic acid. The mixture was left to stir at room temperature for 48 hours. Subsequent purification by kugelrohr (120 °C, 30 mbar) gave the desired amine as a colourless liquid (1.41 g, 82%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2959, 2926, 2863, 1459, 1380;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.45 (2 H, d,  $J = 5.6$  Hz,  $\text{H}_{7a}$ ), 4.35 (2 H, d,  $J = 5.6$  Hz,  $\text{H}_{7b}$ ), 2.75 (2 H, s,  $\text{H}_5$ ), 2.32 (1 H, qt,  $J = 5.9$  Hz,  $\text{H}_1$ ), 1.45 – 1.35 (4 H, m,  $\text{H}_2$ ), 1.28 (3 H, s,  $\text{H}_8$ ), 1.02 (1 H, br s,  $\text{H}_4$ ), 0.87 (6 H, t,  $J = 7.40$  Hz,  $\text{H}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 81.4 ( $\text{C}_7$ ), 60.6 ( $\text{C}_1$ ), 54.3 ( $\text{C}_5$ ), 39.8 ( $\text{C}_6$ ), 26.1 ( $\text{C}_2$ ), 22.0 ( $\text{C}_8$ ), 10.0 ( $\text{C}_3$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  172.1698,  $\text{C}_{10}\text{H}_{22}\text{ON}$  requires 172.1696.

*N*-(adamantan-1-ylmethyl)pentan-3-amine **527c**

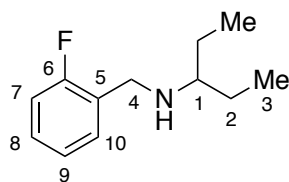
To a solution of adamant-1-ylmethylamine (1.00 g, 6 mmol) and 3-pentanone (0.57 mL, 6.6 mmol) in anhydrous dichloromethane (25 mL) under  $\text{N}_2$ , was added freshly dried 4Å MS (600 mg). The

reaction was subsequently allowed to stir at room temperature for 24 hours. After such time, an additional portion of 4Å MS (600 mg) was added and the mixture left to stir for a further 24 hours. The reaction mixture was then cooled to 0 °C and sodium triacetoxyborohydride (1.70 g, 8 mmol) was added portion-wise. The mixture was left to warm to room temperature over 2 hours and quenched with 1M aqueous NaOH (50 mL). The organic layer was removed, washed with brine, dried over MgSO<sub>4</sub> and removed *in vacuo*. The resulting oil was purified by flash column chromatography (gradient elution: 100% petroleum ether to 20% ethyl acetate in petroleum ether) to yield the desired amine as a colourless oil (1.33 g, 94%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.15; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2959, 2898, 2846, 1451, 1379, 1345, 1316; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 2.25 (1 H, qt, *J* = 6.0 Hz, H<sub>1</sub>), 2.18 (2 H, s, H<sub>4</sub>), 1.95 (3 H, br s, H<sub>7</sub>), 1.67 (6 H, q<sub>app</sub>, *J* = 12.0 Hz, H<sub>8</sub>), 1.52 (6 H, d, *J* = 2.4 Hz, H<sub>6</sub>), 1.42 – 1.34 (4 H, m, H<sub>2</sub>), 0.87 (6 H, t, *J* = 7.2 Hz, H<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 61.1 (C<sub>1</sub>), 59.9 (C<sub>4</sub>), 41.1 (C<sub>6</sub>), 37.5 (C<sub>8</sub>), 33.6 (C<sub>5</sub>), 28.7 (C<sub>7</sub>), 26.2 (C<sub>2</sub>), 10.3 (C<sub>3</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 236.2372, C<sub>16</sub>H<sub>30</sub>N requires 236.2373.

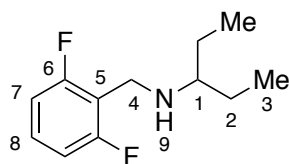
*N*-((trimethylsilyl)methyl)pentan-3-amine **527d**



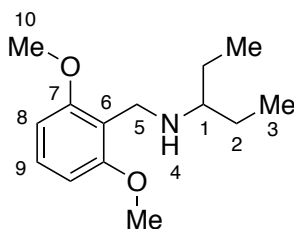
To a solution of 3-aminopentane (2.88 g, 33 mmol) in anhydrous DMSO (15 mL) was added (chloromethyl)trimethylsilane (1.84 g, 15 mmol) dropwise. The mixture was heated at 90 °C for 20 hours after which time the reaction mixture was allowed to cool and quenched with water (50 mL). The mixture was extracted with diethyl ether (2 x 50 mL) and the organics combined, washed with 1% Na<sub>2</sub>CO<sub>3</sub> solution (2 x 50 mL), brine (50 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. The organics were removed *in vacuo* and the resulting oil purified by kugelrohr (120 °C, 50 mbar) to yield the desired compound as a colourless liquid (1.08 g, 42%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2957, 2876, 2773, 1459, 1379, 1247; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 2.24 (1 H, qt, *J* = 6.0 Hz, H<sub>1</sub>), 1.97 (2 H, s, H<sub>4</sub>), 1.40 (4 H, qt, *J* = 7.5 Hz, H<sub>2</sub>), 0.85 (6 H, t, *J* = 7.5 Hz, H<sub>3</sub>), 0.04 (9 H, s, H<sub>5</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 63.5 (C<sub>1</sub>), 36.1 (C<sub>4</sub>), 25.3 (C<sub>2</sub>), 10.0 (C<sub>3</sub>), -2.6 (C<sub>5</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 174.1668, C<sub>9</sub>H<sub>34</sub>NSi requires 174.1673.

*N*-(2-fluorobenzyl)pentan-3-amine **529a**

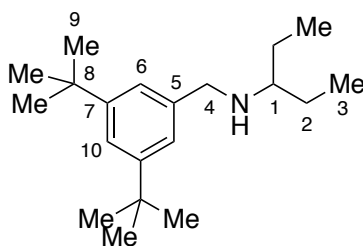
General procedure D was applied to 2-fluorobenzaldehyde (2.11 g, 17 mmol) and 3-aminopentane (1.48 g, 17 mmol) in dichloromethane (75 mL). The mixture was left to stir at room temperature for 72 hours. Purification by kugelrohr (90 °C, 3 mbar) gave the desired compound as a colourless liquid (0.90 g, 30%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2962, 2932, 2875, 1617, 1586, 1489, 1456, 1381, 1228;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.35 (1 H, dt,  $J = 1.7, 7.6$  Hz,  $\text{H}_{10}$ ), 7.25 – 7.19 (1 H, m,  $\text{H}_8$ ), 7.09 (1 H, app t,  $J = 7.5$  Hz,  $\text{H}_9$ ), 7.02 (1 H, app t,  $J = 9.7$  Hz,  $\text{H}_7$ ), 3.81 (2 H, s,  $\text{H}_4$ ), 2.40 (1 H, qt,  $J = 5.8$  Hz,  $\text{H}_1$ ), 1.50 – 1.42 (4 H, m,  $\text{H}_2$ ), 0.88 (6 H, t,  $J = 7.5$  Hz,  $\text{H}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 161.4 (d,  $^1J_{\text{C-F}} = 244.9$  Hz,  $\text{C}_6$ ), 130.6 (d,  $^3J_{\text{C-F}} = 4.9$  Hz,  $\text{C}_{10}$ ), 128.6 (d,  $^3J_{\text{C-F}} = 8.3$  Hz,  $\text{C}_8$ ), 128.0 (d,  $^2J_{\text{C-F}} = 15.0$  Hz,  $\text{C}_5$ ), 124.1 (d,  $^4J_{\text{C-F}} = 3.4$  Hz,  $\text{C}_9$ ), 115.3 (d,  $^2J_{\text{C-F}} = 22.1$  Hz,  $\text{C}_7$ ), 59.4 ( $\text{C}_1$ ), 44.8 (d,  $^3J_{\text{C-F}} = 3.0$  Hz,  $\text{C}_4$ ), 25.9 ( $\text{C}_2$ ), 9.9 ( $\text{C}_3$ );  $^{19}\text{F}\{^1\text{H}\}$  NMR (377 MHz,  $\text{CDCl}_3$ )  $\delta$ : –119.9;  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  196.1491,  $\text{C}_{12}\text{H}_{19}\text{FN}$  requires 196.1496.

*N*-(2,6-difluorobenzyl)pentan-3-amine **529d**

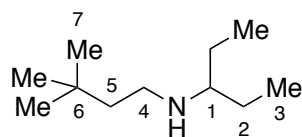
General procedure D was applied to 2,6-difluorobenzylamine (1.00 g, 7 mmol) and 3-pentanone (0.91 g, 10.5 mmol) in dichloromethane (40 mL). The mixture was left to stir at room temperature for 72 hours. Purification by kugelrohr (90 °C, 3 mbar) gave the desired amine as a colourless liquid (1.20 g, 81%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2962, 2931, 2876, 1624, 1592, 1468, 1381;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.18 (1 H, tt,  $J = 6.4, 6.6$  Hz,  $\text{H}_8$ ), 6.86 (2 H, t,  $J = 7.8$  Hz,  $\text{H}_7$ ), 3.86 (2 H, s,  $\text{H}_4$ ), 2.32 (1 H, qt,  $J = 5.7$  Hz,  $\text{H}_1$ ), 1.49 – 1.41 (5 H, m,  $\text{H}_2, \text{H}_9$ ), 0.86 (6 H, t,  $J = 7.5$  Hz,  $\text{H}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 162.0 (dd,  $^1J_{\text{C-F}} = 246.9$  Hz,  $^3J_{\text{C-F}} = 9.0$  Hz,  $\text{C}_6$ ), 128.7 (t,  $^3J_{\text{C-F}} = 10.3$  Hz,  $\text{C}_8$ ), 116.6 (t,  $^2J_{\text{C-F}} = 20.2$  Hz,  $\text{C}_5$ ), 111.3 (m,  $\text{C}_7$ ), 59.2 ( $\text{C}_1$ ), 38.2 (t,  $^3J_{\text{C-F}} = 2.9$  Hz,  $\text{C}_4$ ), 25.9 ( $\text{C}_2$ ), 9.9 ( $\text{C}_3$ );  $^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$ : –116.8;  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  214.1400,  $\text{C}_{12}\text{H}_{18}\text{F}_2\text{N}$  requires 214.1402.

*N*-(2,6-dimethoxybenzyl)pentan-3-amine **529f**

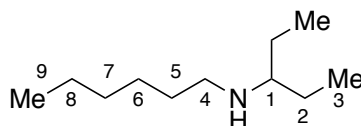
General procedure D was applied to 2,6-dimethoxybenzaldehyde (2.50 g, 15 mmol) and 3-aminopentane (1.31 g, 15 mmol) in dichloromethane (60 mL). The mixture was left to stir at room temperature for 48 hours. Purification by kugelrohr (142 °C, 0.7 mbar) gave the desired compound as a colourless oil (2.38 g, 67%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2958, 2935, 2874, 2836, 1594, 1473, 1435, 1379, 1321, 1258, 1222;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.16 (1 H, t,  $J = 8.4$  Hz,  $\text{H}_9$ ), 6.53 (2 H, d,  $J = 8.4$  Hz,  $\text{H}_8$ ), 3.82 (2 H, s,  $\text{H}_5$ ), 3.81 (6 H, s,  $\text{H}_{10}$ ), 2.25 (1 H, qt,  $J = 6.0$  Hz,  $\text{H}_1$ ), 1.82 (1 H, br s,  $\text{H}_4$ ), 1.48 – 1.41 (4 H, m,  $\text{H}_2$ ), 0.85 (6 H, t,  $J = 7.5$  Hz,  $\text{H}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 158.8 ( $\text{C}_7$ ), 128.1 ( $\text{C}_9$ ), 117.1 ( $\text{C}_6$ ), 103.7 ( $\text{C}_8$ ), 59.4 ( $\text{C}_1$ ), 55.7 ( $\text{C}_{10}$ ), 39.0 ( $\text{C}_5$ ), 26.2 ( $\text{C}_2$ ), 10.2 ( $\text{C}_3$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  238.1805,  $\text{C}_{14}\text{H}_{24}\text{O}_2\text{N}$  requires 238.1802.

*N*-(3,5-di-*tert*-butylbenzyl)pentan-3-amine **529g**

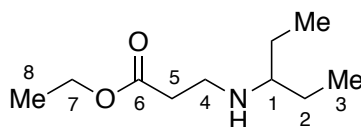
General procedure D was applied to 3,5-di-*tert*-butylbenzaldehyde (2.18 g, 10 mmol) and 3-aminopentane (0.87 g, 10 mmol) in dichloromethane (75 mL). The mixture was left to stir at room temperature for 72 hours. Subsequent purification by kugelrohr (123 °C, 0.38 mbar) gave the desired product as a colourless liquid (1.55 g, 54%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2956, 2872, 1600, 1460, 1393, 1362, 1248;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.31 (1 H, t,  $J = 1.8$  Hz,  $\text{H}_{10}$ ), 7.17 (2 H, d,  $J = 1.8$  Hz,  $\text{H}_6$ ), 3.77 (2 H, s,  $\text{H}_4$ ), 2.44 (1 H, qt,  $J = 5.9$  Hz,  $\text{H}_1$ ), 1.47 (4 H, m,  $\text{H}_2$ ), 1.33 (18 H, s,  $\text{H}_9$ ), 0.91 (6 H, t,  $J = 7.4$  Hz,  $\text{H}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 150.7 ( $\text{C}_7$ ), 140.2 ( $\text{C}_5$ ), 122.3 ( $\text{C}_6$ ), 120.8 ( $\text{C}_{10}$ ), 59.4 ( $\text{C}_1$ ), 51.7 ( $\text{C}_4$ ), 34.8 ( $\text{C}_8$ ), 31.5 ( $\text{C}_9$ ), 25.9 ( $\text{C}_2$ ), 10.0 ( $\text{C}_3$ ); HRMS found  $[\text{M} + \text{H}]^+$  290.2841,  $\text{C}_{20}\text{H}_{36}\text{N}$  requires 290.2842.

*N*-(3,3-dimethylbutyl)pentan-3-amine **533a**

General procedure D was applied with 3,3-dimethylbutyraldehyde (2.50 g, 25 mmol) and 3-aminopentane (2.18 g, 25 mmol) in dichloromethane (100 mL). The mixture was left to stir at room temperature for 72 hours. Purification by kugelrohr (90 °C, 20 mbar) gave the desired product as a colourless liquid (3.21 g, 75%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2956, 2873, 1462, 1364, 1250;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.57 – 2.53 (2 H, m,  $\text{H}_4$ ), 2.35 (1 H, qt,  $J = 5.8$  Hz,  $\text{H}_1$ ), 1.45 – 1.36 (6 H, m,  $\text{H}_2$ ,  $\text{H}_5$ ), 0.90 (9 H, s,  $\text{H}_7$ ), 0.87 (6 H, t,  $J = 7.5$  Hz,  $\text{H}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 60.5 ( $\text{C}_1$ ), 44.8 ( $\text{C}_5$ ), 43.5 ( $\text{C}_4$ ), 30.0 ( $\text{C}_6$ ), 29.8 ( $\text{C}_7$ ), 26.0 ( $\text{C}_2$ ), 10.1 ( $\text{C}_3$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  172.2055,  $\text{C}_{11}\text{H}_{26}\text{N}$  requires 172.2060.

*N*-(pentan-3-yl)hexan-1-amine **533b**

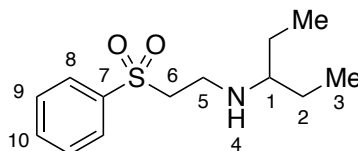
General procedure D was applied to 3-pentanone (2.15 g, 25 mmol) and *n*-hexylamine (2.53 g, 25 mmol) in dichloromethane (100 mL). The mixture was left to stir at room temperature for 72 hours. Subsequent purification by kugelrohr (89 °C, 12 mbar) gave the desired amine as a colourless liquid (2.91 g, 68%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2958, 2924, 2874, 2858, 1459, 1379;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.53 (2 H, t,  $J = 7.8$  Hz,  $\text{H}_4$ ), 2.32 (1 H, qt,  $J = 5.5$  Hz,  $\text{H}_1$ ), 1.46 – 1.37 (6 H, m,  $\text{H}_2$ ,  $\text{H}_5$ ), 1.32 – 1.25 (6 H, m,  $\text{H}_6$ ,  $\text{H}_7$ ,  $\text{H}_8$ ), 0.88 – 0.84 (9 H, m,  $\text{H}_3$ ,  $\text{H}_9$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 60.1 ( $\text{C}_1$ ), 47.3 ( $\text{C}_4$ ), 31.8 ( $\text{C}_7$ ), 30.5 ( $\text{C}_5$ ), 27.1 ( $\text{C}_6$ ), 25.9 ( $\text{C}_2$ ), 22.6 ( $\text{C}_8$ ), 14.0 ( $\text{C}_9$ ), 9.9 ( $\text{C}_3$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  172.2060,  $\text{C}_{11}\text{H}_{26}\text{N}$  requires 172.2060.

*Ethyl 3-(pentan-3-ylamino)propanoate* **533c**

A solution of ethyl acrylate (1.50 g, 15 mmol) in absolute ethanol (7 mL) was added slowly dropwise to a solution of 3-aminopentane (2.61 g, 30 mmol) in absolute ethanol (20 mL) at 0 °C. The solution was warmed to room temperature over 16 hours and the solvent removed *in vacuo*. The resulting oil was purified by kugelrohr (115 °C, 20 mbar) to yield the desired product as a colourless liquid (2.43

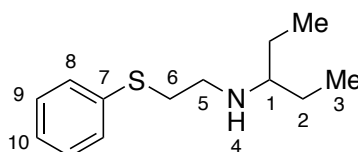
g, 86%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2962, 2933, 2876, 1733, 1461, 1373, 1350;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.13 (2 H, q,  $J = 7.2$  Hz,  $\text{H}_7$ ), 2.83 (2 H, t,  $J = 6.5$  Hz,  $\text{H}_4$ ), 2.48 (2 H, t,  $J = 6.5$  Hz,  $\text{H}_5$ ), 2.35 (1 H, qt,  $J = 5.8$  Hz,  $\text{H}_1$ ), 1.40 (4 H, m,  $\text{H}_2$ ), 1.25 (3 H, t,  $J = 7.2$  Hz,  $\text{H}_8$ ), 0.87 (6 H, t,  $J = 7.4$  Hz,  $\text{H}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 173.0 ( $\text{C}_6$ ), 60.4 ( $\text{C}_7$ ), 59.8 ( $\text{C}_1$ ), 42.2 ( $\text{C}_4$ ), 35.2 ( $\text{C}_5$ ), 25.8 ( $\text{C}_2$ ), 14.2 ( $\text{C}_8$ ), 9.9 ( $\text{C}_3$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  188.1640,  $\text{C}_{10}\text{H}_{22}\text{NO}_2$  requires 188.1645.

*N*-(2-(phenylsulfonyl)ethyl)pentan-3-amine **533d**



A solution of phenyl vinyl sulfone (2.50 g, 15 mmol) in absolute ethanol (25 mL) was added slowly dropwise to a solution of 3-aminopentane (2.61 g, 30 mmol) in absolute ethanol (20 mL) at 0 °C. The solution was warmed to room temperature over 16 hours and the solvent removed *in vacuo*. The resulting oil was purified by kugelrohr (165 °C, 0.47 mbar) to yield the desired compound as a colourless liquid (2.35 g, 61%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2962, 2931, 2875, 1586, 1461, 1447, 1382, 1305;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.92 (2 H, app d,  $J = 8.0$  Hz,  $\text{H}_8$ ), 7.66 (1 H, app t,  $J = 7.3$  Hz,  $\text{H}_{10}$ ), 7.57 (2 H, app t,  $J = 8.0$  Hz,  $\text{H}_9$ ), 3.28 (2 H, t,  $J = 6.3$  Hz,  $\text{H}_5$ ), 2.98 (2 H, t,  $J = 6.3$  Hz,  $\text{H}_6$ ), 2.31 (1 H, qt,  $J = 6.3$  Hz,  $\text{H}_1$ ), 1.50 (1 H, br s,  $\text{H}_4$ ), 1.40 – 1.31 (4 H, m,  $\text{H}_2$ ), 0.83 (6 H, t,  $J = 7.3$  Hz,  $\text{H}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 139.40 ( $\text{C}_7$ ), 133.8 ( $\text{C}_{10}$ ), 129.3 ( $\text{C}_9$ ), 128.0 ( $\text{C}_8$ ), 59.7 ( $\text{C}_1$ ), 56.6 ( $\text{C}_5$ ), 40.4 ( $\text{C}_6$ ), 25.6 ( $\text{C}_2$ ), 9.7 ( $\text{C}_3$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  256.1359,  $\text{C}_{13}\text{H}_{22}\text{NO}_2\text{S}$  requires 256.1366.

*N*-(2-(phenylthio)ethyl)pentan-3-amine **533e**

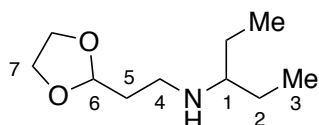


To a solution of 3-aminopentane (2.53 g, 29 mmol) in anhydrous DMSO (15 mL) was added 2-bromoethyl phenyl sulfide (2.88 g, 13 mmol) dropwise. The mixture was heated at 90 °C for 18 hours after which time the reaction mixture was allowed to cool and quenched with water (50 mL). The mixture was extracted with diethyl ether (2 x 50 mL) and the organics combined, washed with 1% aqueous  $\text{Na}_2\text{CO}_3$  solution (2 x 50 mL), brine (50 mL) and dried over  $\text{Na}_2\text{SO}_4$ . The organics were removed *in vacuo* and the resulting oil purified by kugelrohr (110 °C, 0.44 mbar) to yield the desired product as a colourless liquid (>95% pure by  $^1\text{H}$  NMR) (0.95 g, 33%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2960, 2924, 2873, 1584, 1480, 1459, 1439, 1379, 1280, 1225.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.37 – 7.35



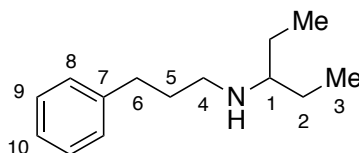
(2 H, m, H<sub>9</sub>), 7.30 – 7.26 (2 H, m, H<sub>8</sub>), 7.21 – 7.17 (1 H, m, H<sub>10</sub>), 3.07 (2 H, t,  $J = 6.3$  Hz, H<sub>5</sub>), 2.80 (2 H, t,  $J = 6.5$  Hz, H<sub>6</sub>), 2.34 (1 H, qt,  $J = 5.6$  Hz, H<sub>1</sub>), 1.50 (1 H, br s, H<sub>4</sub>), 1.44 – 1.36 (4 H, m, H<sub>2</sub>), 0.87 (6 H, m,  $J = 7.4$  Hz, H<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 135.9 (C<sub>7</sub>), 129.7 (C<sub>9</sub>), 128.9 (C<sub>8</sub>), 126.2 (C<sub>10</sub>), 59.7 (C<sub>1</sub>), 45.4 (C<sub>6</sub>), 34.7 (C<sub>5</sub>), 25.9 (C<sub>2</sub>), 9.9 (C<sub>3</sub>);  $m/z$  HRMS found  $[M + H]^+$  224.1466, C<sub>13</sub>H<sub>22</sub>NS requires 224.1467.

*N*-(2-(1,3-dioxolan-2-yl)ethyl)pentan-3-amine **533f**



To a solution of 3-aminopentane (2.88 g, 33 mmol) in anhydrous DMSO (15 mL) was added 2-(2-bromoethyl)-1,3-dioxolane (2.72 g, 15 mmol) dropwise. The mixture was heated at 90 °C for 18 hours after which time the reaction mixture was allowed to cool and quenched with water (50 mL). The mixture was extracted with diethyl ether (2 x 50 mL) and the organics combined, washed with 1% aqueous Na<sub>2</sub>CO<sub>3</sub> solution (2 x 50 mL), brine (50 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. The organics were removed *in vacuo* and the resulting oil purified by kugelrohr (130 °C, 15 mbar) to yield the desired product as a colourless liquid (1.27 g, 45%). IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2958, 2932, 2875, 1461, 1408, 1381; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 4.93 (1 H, t,  $J = 4.7$  Hz, H<sub>6</sub>), 3.98 – 3.82 (4 H, m, H<sub>7</sub>), 2.70 (2 H, t,  $J = 6.8$  Hz, H<sub>4</sub>), 2.33 (1 H, qt,  $J = 5.9$  Hz, H<sub>1</sub>), 1.86 (2 H, dt,  $J = 4.7, 6.8$  Hz, H<sub>5</sub>), 1.41 (4 H, m, H<sub>2</sub>), 0.86 (6 H, t,  $J = 7.5$  Hz, H<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 103.9 (C<sub>6</sub>), 64.8 (C<sub>7</sub>), 60.2 (C<sub>1</sub>), 42.1 (C<sub>4</sub>), 34.2 (C<sub>5</sub>), 25.8 (C<sub>2</sub>), 9.9 (C<sub>3</sub>);  $m/z$  HRMS found  $[M + H]^+$  188.1641, C<sub>10</sub>H<sub>22</sub>NO<sub>2</sub> requires 188.1645.

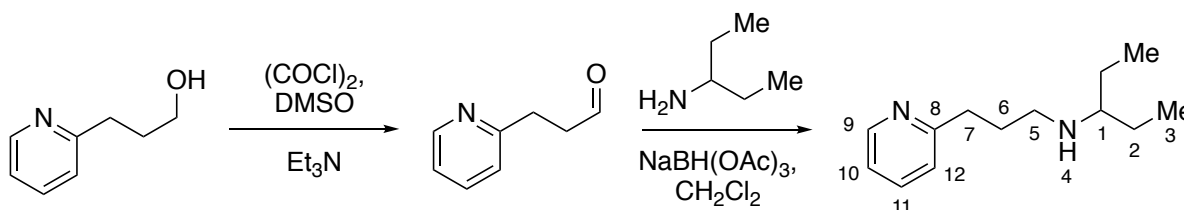
*N*-(3-phenylpropyl)pentan-3-amine **535a**



General procedure D was applied to 3-phenylpropan-1-amine (3.38 g, 25 mmol) and 3-pentanone (2.15 g, 25 mmol) in dichloromethane (100 mL). The mixture was left to stir at room temperature for 72 hours. Subsequent purification by kugelrohr (115 °C, 8 mbar) gave the desired compound as a colourless liquid (3.38 g, 66%). IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2959, 2929, 2869, 1604, 1496, 1455, 1379, 1156, 1099; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.29 – 7.26 (2 H, m, H<sub>9</sub>), 7.20 – 7.16 (3 H, m, H<sub>8</sub> and H<sub>10</sub>), 2.67 (2 H, t,  $J = 8.1$  Hz, H<sub>6</sub>), 2.61 (2 H, t,  $J = 7.3$  Hz, H<sub>4</sub>), 2.35 (1 H, qt,  $J = 5.9$  Hz, H<sub>1</sub>), 1.81 (2

H, qt,  $J = 7.5$  Hz, H<sub>5</sub>), 1.44 – 1.38 (4 H, m, H<sub>2</sub>), 0.87 (6 H, t,  $J = 7.4$  Hz, H<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$ : 142.3 (C<sub>7</sub>), 128.4 (C<sub>8</sub>), 128.3 (C<sub>9</sub>), 125.7 (C<sub>10</sub>), 60.0 (C<sub>1</sub>), 46.7 (C<sub>4</sub>), 33.8 (C<sub>6</sub>), 32.1 (C<sub>5</sub>), 25.8 (C<sub>2</sub>), 9.9 (C<sub>3</sub>); m/z HRMS found  $[M + H]^+$  206.1905, C<sub>14</sub>H<sub>24</sub>N requires 206.1903.

### *N*-(3-(pyridin-2-yl)propyl)pentan-3-amine **535b**



#### Step 1

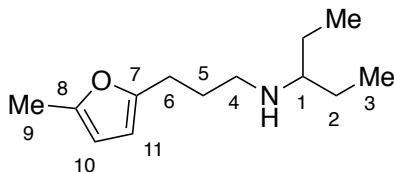
To a dry 500 mL round-bottomed flask equipped with pressure-equalizing addition funnel containing oxalyl chloride (5.09 g, 40.1 mmol) in anhydrous dichloromethane (50 mL) was added a solution of DMSO (6.27 g, 80.3 mmol) in anhydrous dichloromethane (50 mL) dropwise at  $-78$  °C under N<sub>2</sub>. The solution was allowed to stir at  $-78$  °C for 15 minutes after which time a solution of 3-(pyridin-2-yl)propan-1-ol (5.01 g, 36.5 mmol) in anhydrous dichloromethane (50 mL) was added dropwise at  $-78$  °C and stirred for 1 hour. Subsequently, triethylamine (9.13 g, 91.2 mmol) was added at  $-78$  °C and the mixture was warmed to room temperature. The reaction mixture was washed with water (3 x 100 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed *in vacuo* to give 3-(pyridin-2-yl)propionaldehyde as a dark viscous oil (3.00 g, 61 %). The product was used in the next step without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 9.87 (1 H, s), 8.50 (1 H, d,  $J = 4.4$  Hz), 7.59 (1 H, dt,  $J = 1.8, 7.7$  Hz), 7.18 (1 H, d,  $J = 7.7$  Hz), 7.11 (1 H, dd,  $J = 5.1, 7.2$  Hz), 3.13 (2 H, t,  $J = 6.9$  Hz), 2.94 (2 H, t,  $J = 7.1$  Hz). Data consistent with literature<sup>633</sup>.

#### Step 2

General procedure D was applied with 3-(pyridin-2-yl)propionaldehyde from Step 1 (3.00 g, 22.2 mmol) and 3-aminopentane (1.93 g, 22.2 mmol) in dichloromethane (150 mL). The mixture was left to stir at room temperature for 24 hours. The resulting oil was purified by kugelrohr (100 °C, 0.40 mbar) to give the desired product as a colourless liquid (2.43 g, 53%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2959, 2929, 2874, 1590, 1569, 1474, 1569, 1474, 1461, 1434, 1379, 1297, 1149; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.47 (1 H, d,  $J = 4.4$  Hz, H<sub>9</sub>), 7.54 (1 H, dt,  $J = 1.7, 7.7$  Hz, H<sub>11</sub>), 7.12 (1 H, d,  $J = 7.7$  Hz, H<sub>12</sub>), 7.05 (1 H, dd,  $J = 5.4, 7.1$  Hz, H<sub>10</sub>), 2.81 (2 H, t,  $J = 7.5$  Hz, H<sub>7</sub>), 2.60 (2 H, t,  $J = 7.1$  Hz, H<sub>5</sub>), 2.33 (1 H, qt,  $J = 6.0$  Hz, H<sub>1</sub>), 1.88 (2 H, qt,  $J = 7.3$  Hz, H<sub>6</sub>), 1.53 (1 H, br s, H<sub>4</sub>), 1.37 (4 H, qt,  $J = 7.1$  Hz, H<sub>2</sub>), 0.83 (6 H, t,  $J = 7.5$  Hz, H<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 162.0 (C<sub>8</sub>), 149.3 (C<sub>9</sub>),

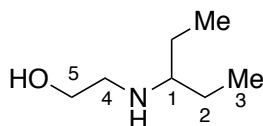
136.4 (C<sub>11</sub>), 122.8 (C<sub>12</sub>), 121.0 (C<sub>10</sub>), 60.0 (C<sub>1</sub>), 46.6 (C<sub>5</sub>), 36.3 (C<sub>7</sub>), 30.5 (C<sub>6</sub>), 25.9 (C<sub>2</sub>), 9.9 (C<sub>3</sub>); m/z HRMS found [M + H]<sup>+</sup> 207.1855, C<sub>13</sub>H<sub>23</sub>N<sub>2</sub> requires 207.1856.

*N*-(3-(5-methylfuran-2-yl)propyl)pentan-3-amine **535c**

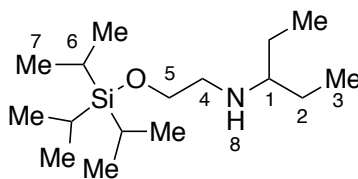


General procedure D was applied to 3-(5-methylfuran-2-yl)propanal (2.76 g, 20 mmol) and 3-aminopentane (1.74 g, 20 mmol) in dichloromethane (100 mL). The mixture was left to stir at room temperature for 24 hours. The resulting oil was purified by kugelrohr (90 °C, 0.40 mbar) to give the desired product as a colourless liquid (1.29 g, 31%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2959, 2923, 2875, 1618, 1570, 1459, 1381, 1219, 1157, 1099, 1019; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 5.85 – 5.82 (2 H, m, H<sub>10</sub> and H<sub>11</sub>), 2.64 – 2.59 (4 H, m, H<sub>4</sub> and H<sub>6</sub>), 2.35 (1 H, qt,  $J$  = 6.1 Hz, H<sub>1</sub>), 2.24 (3 H, s, H<sub>9</sub>), 1.78 (2 H, qt,  $J$  = 7.0 Hz, H<sub>5</sub>), 1.44 – 1.36 (4 H, m, H<sub>2</sub>), 0.87 (6 H, t,  $J$  = 7.4 Hz, H<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 154.3 (C<sub>7</sub>), 150.3 (C<sub>8</sub>), 105.9 (C<sub>10</sub>), 105.5 (C<sub>11</sub>), 60.1 (C<sub>1</sub>), 46.6 (C<sub>4</sub>), 29.1 (C<sub>5</sub>), 26.1 (C<sub>6</sub>), 26.0 (C<sub>2</sub>), 13.6 (C<sub>9</sub>), 10.0 (C<sub>3</sub>); m/z HRMS found [M + H]<sup>+</sup> 210.1849, C<sub>13</sub>H<sub>24</sub>NO requires 210.1852.

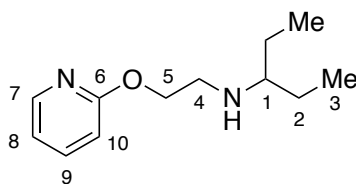
2-(pentan-3-ylamino)ethanol **689**



General procedure D was applied to ethanolamine (3.36 g, 55 mmol) and 3-pentanone (4.30 g, 50 mmol) in dichloromethane (200 mL) without acetic acid. The mixture was left to stir at room temperature for 72 hours. Subsequent purification by kugelrohr (105 °C, 10 mbar) gave the desired amine as a colourless liquid (3.39 g, 52%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3305 (br), 2962, 2932, 2876, 1460, 1380, 1360, 1216, 1152, 1062; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 3.59 (2 H, t,  $J$  = 5.2 Hz, H<sub>5</sub>), 2.73 (2 H, t,  $J$  = 5.2 Hz, H<sub>4</sub>), 2.36 (1 H, qt,  $J$  = 5.9 Hz, H<sub>1</sub>), 1.41 (4 H, m, H<sub>2</sub>), 0.87 (6 H, t,  $J$  = 7.5 Hz, H<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 61.2 (C<sub>5</sub>), 59.7 (C<sub>1</sub>), 48.1 (C<sub>4</sub>), 26.0 (C<sub>2</sub>), 9.9 (C<sub>3</sub>); m/z HRMS found [M + H]<sup>+</sup> 132.1382, C<sub>7</sub>H<sub>18</sub>ON requires 132.1383.

*N*-(2-((triisopropylsilyl)oxy)ethyl)pentan-3-amine **537a**

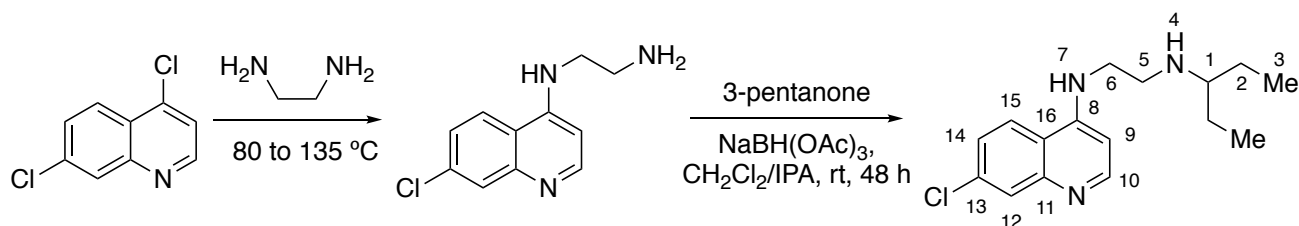
To a solution of 2-(pentan-3-ylamino)ethanol **689** (0.55 g, 4.2 mmol) and triethylamine (1.70 g, 16.8 mmol, 4.0 equiv) in anhydrous dichloromethane (15 mL) at 0 °C was added triisopropylsilyl trifluoromethanesulfonate (1.61 g, 5.25 mmol, 1.25 equiv) dropwise over 15 minutes under N<sub>2</sub>. The solution was allowed to warm to room temperature over 16 hours and quenched with sat. aqueous NaHCO<sub>3</sub> (15 mL). The aqueous layer was extracted with dichloromethane (2 x 15 mL) and the organics combined, washed with brine (30 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed *in vacuo* and purification by flash column chromatography (gradient elution: 100% petroleum ether to 30% ethyl acetate in petroleum ether with 1% Et<sub>3</sub>N) and kugelrohr (100 °C, 0.44 mbar) to give the desired amine as a colourless oil (0.77 g, 64%). IR  $\nu_{\text{max}}$ /cm<sup>-1</sup> (film): 2959, 2941, 2866, 1462, 1382, 1248; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 3.80 (2 H, t, *J* = 5.4 Hz, H<sub>5</sub>), 2.69 (2 H, t, *J* = 5.4 Hz, H<sub>4</sub>), 2.36 (1 H, qt, *J* = 6.2 Hz, H<sub>1</sub>), 1.60 (1 H, br s, H<sub>8</sub>), 1.46 – 1.39 (4 H, m, H<sub>2</sub>), 1.06 – 1.05 (21 H, m, H<sub>6</sub> and H<sub>7</sub>), 0.88 (6 H, t, *J* = 7.4 Hz, H<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 62.8 (C<sub>5</sub>), 60.1 (C<sub>1</sub>), 49.4 (C<sub>4</sub>), 26.0 (C<sub>2</sub>), 18.0 (C<sub>7</sub>), 11.9 (C<sub>6</sub>), 9.9 (C<sub>3</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 288.2715, C<sub>16</sub>H<sub>38</sub>ONSi requires 288.2717.

*N*-(2-(pyridin-2-yloxy)ethyl)pentan-3-amine **537b**

To a dry 100 mL 2-neck round bottomed-flask equipped with condenser was added 2-(pentan-3-ylamino)ethanol **689** (1.31 g, 10 mmol) in anhydrous 1,4-dioxane (20 mL) under N<sub>2</sub>. Sodium hydride (60% dispersion in mineral oil) (0.40 g, 10 mmol) was added portion-wise and the mixture refluxed for 30 minutes. After such time, the reaction mixture was allowed to cool to room temperature and 2-chloropyridine (1.14 g, 10 mmol) was added dropwise. The mixture was subsequently refluxed for a further 16 hours and cooled to room temperature. The solvent was removed *in vacuo* and the residue taken up in dichloromethane (25 mL). The organics were washed with water (2 x 25 mL), brine (25 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed *in vacuo* and the resulting oil purified by kugelrohr (95 °C, 0.45 mbar) to yield the desired product as a colourless oil (1.46 g, 70%). IR

$\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2959, 2982, 2875, 1596, 1571, 1475, 1431, 1381, 1310, 1286, 1270, 1142;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.13 (1 H, dd,  $J = 1.9, 5.1$  Hz,  $\text{H}_7$ ), 7.55 (1 H, ddd,  $J = 1.9, 7.2, 8.3$  Hz,  $\text{H}_9$ ), 6.84 (1 H, ddd,  $J = 0.8, 5.1, 7.2$  Hz,  $\text{H}_8$ ), 6.73 (1 H, d,  $J = 8.3$  Hz,  $\text{H}_{10}$ ), 4.39 (2 H, t,  $J = 5.5$  Hz,  $\text{H}_5$ ), 2.96 (2 H, t,  $J = 5.5$  Hz,  $\text{H}_4$ ), 2.42 (1 H, qt,  $J = 6.0$  Hz,  $\text{H}_1$ ), 1.48 – 1.40 (4 H, m,  $\text{H}_2$ ), 0.88 (6 H, t,  $J = 7.53$ ,  $\text{H}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 163.8 ( $\text{C}_6$ ), 146.9 ( $\text{C}_7$ ), 138.5 ( $\text{C}_9$ ), 116.7 ( $\text{C}_8$ ), 111.0 ( $\text{C}_{10}$ ), 65.7 ( $\text{C}_5$ ), 59.7 ( $\text{C}_1$ ), 45.9 ( $\text{C}_4$ ), 25.9 ( $\text{C}_2$ ), 9.9 ( $\text{C}_3$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  209.1645,  $\text{C}_{12}\text{H}_{21}\text{N}_2\text{O}$  requires 209.1648.

$N^1$ -(7-chloroquinolin-4-yl)- $N^2$ -(pentan-3-yl)ethane-1,2-diamine **537i**



### Step 1

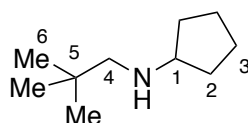
A mixture of 4,7-dichloroquinoline (1.98 g, 10 mmol) and ethane-1,2-diamine (3.00 g, 50 mmol) were heated at 80 °C for 1 hour without stirring and then at 135 °C for 3 hours with stirring. After such time the reaction mixture was cooled to room temperature and poured over 10% NaOH (60 mL). The mixture was extracted with ethyl acetate (3 x 75 mL) and dried over  $\text{Na}_2\text{SO}_4$ . The organics were removed *in vacuo* and the residue purified by recrystallization from ethyl acetate to give  $N^1$ -(7-chloroquinolin-4-yl)ethane-1,2-diamine as pale yellow crystals (1.35 g, 61%).  $^1\text{H}$  NMR (400.1 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.37 (1 H, d,  $J = 5.9$  Hz), 8.12 (1 H, d,  $J = 9.0$  Hz), 7.78 (1 H, d,  $J = 2.1$  Hz), 7.41 (1 H, dd,  $J = 2.1, 9.0$  Hz), 6.58 (1 H, d,  $J = 5.8$  Hz), 3.45 (2 H, t,  $J = 6.4$  Hz), 2.98 (2 H, t,  $J = 6.4$  Hz);  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  222.0793  $\{^{35}\text{Cl}\}$ ,  $\text{C}_{11}\text{H}_{13}\text{ClN}_3$  requires 222.0793  $\{^{35}\text{Cl}\}$ . Data consistent with literature<sup>634</sup>.

### Step 2

General procedure D was applied with  $N^1$ -(7-chloroquinolin-4-yl)ethane-1,2-diamine from Step 1 (1.11 g, 5 mmol) and 3-pentanone (0.43 g, 5 mmol) in 1:1 dichloromethane/IPA (20 mL) without acetic acid. The mixture was left to stir at room temperature for 48 hours. The resulting solid was purified by flash column chromatography (10% methanol in dichloromethane) to give the desired product as a pale yellow solid (0.75 g, 51%).  $R_f$  (10% methanol in dichloromethane): 0.18; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3230, 3067, 2954, 1613, 1580, 1484, 1456, 1433, 1386, 1369, 1346, 1330, 1282, 1228, 1136;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.51 (1 H, d,  $J = 8.5$  Hz,  $\text{H}_{10}$ ), 7.93 (1 H, d,  $J = 2.1$  Hz,

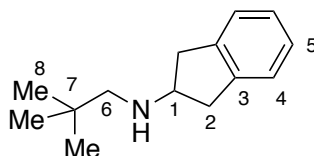
H<sub>12</sub>), 7.68 (1 H, d,  $J = 7.7$  Hz, H<sub>15</sub>), 7.35 (1 H, dd,  $J = 2.1, 7.7$  Hz, H<sub>14</sub>), 6.36 (1 H, d,  $J = 8.5$  Hz, H<sub>9</sub>), 6.06 (1 H, br s, H<sub>7</sub>), 3.29 – 3.26 (2 H, m, H<sub>6</sub>), 3.01 – 2.99 (2 H, m, H<sub>5</sub>), 2.43 (1 H, qt,  $J = 5.8$  Hz, H<sub>1</sub>), 1.51 – 1.41 (4 H, m, H<sub>2</sub>), 1.34 (1 H, br s, H<sub>4</sub>), 0.92 (6 H, t,  $J = 7.3$  Hz, H<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 152.2 (C<sub>10</sub>), 150.1 (C<sub>11</sub>), 149.3 (C<sub>16</sub>), 134.9 (C<sub>13</sub>), 128.8 (C<sub>12</sub>), 125.3 (C<sub>14</sub>), 121.3 (C<sub>15</sub>), 117.6 (C<sub>8</sub>), 99.3 (C<sub>9</sub>), 59.5 (C<sub>1</sub>), 44.6 (C<sub>5</sub>), 42.5 (C<sub>6</sub>), 26.2 (C<sub>2</sub>), 10.1 (C<sub>3</sub>);  $m/z$  HRMS found  $[M + H]^+$  292.1569 {<sup>35</sup>Cl}, C<sub>16</sub>H<sub>23</sub>ClN<sub>3</sub> requires 292.1575 {<sup>35</sup>Cl}.

#### *N*-neopentylcyclopentanamine **539a**

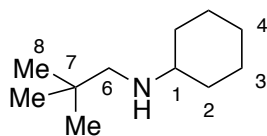


General procedure D was applied to cyclopentanone (2.10 g, 25 mmol) and neopentylamine (2.18 g, 25 mmol) in dichloromethane (100 mL). The mixture was left to stir at room temperature for 72 hours. Purification by kugelrohr (100 °C, 30 mbar) gave the desired amine as a colourless liquid (2.90 g, 75%). IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2951, 2867, 1465, 1395, 1361, 1288; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 2.99 (1 H, qt,  $J = 6.8$  Hz, H<sub>1</sub>), 2.32 (2 H, s, H<sub>4</sub>), 1.86 – 1.78 (2 H, m, H<sub>2a</sub>), 1.72 – 1.62 (2 H, m, H<sub>3a</sub>), 1.56 – 1.48 (2 H, m, H<sub>3b</sub>), 1.33 – 1.24 (2 H, m, H<sub>2b</sub>), 0.89 (9 H, s, H<sub>6</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 61.3 (C<sub>4</sub>), 60.8 (C<sub>1</sub>), 33.4 (C<sub>2</sub>), 31.4 (C<sub>5</sub>), 28.0 (C<sub>6</sub>), 24.2 (C<sub>3</sub>);  $m/z$  HRMS found  $[M + H]^+$  156.1743, C<sub>10</sub>H<sub>22</sub>N requires 156.1747.

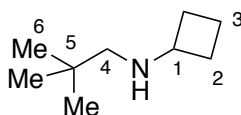
#### *N*-neopentyl-2-indanamine **539b**



General procedure D was applied to 2-indanone (1.98 g, 15 mmol) and neopentylamine (1.31 g, 15 mmol) in dichloromethane (60 mL). The mixture was left to stir at room temperature for 72 hours. Purification by kugelrohr (105 °C, 0.7 mbar) gave the desired product as a colourless oil that darkened on standing (1.09 g, 38%). IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 3021, 2949, 2899, 2835, 1477, 1461, 1394, 1361, 1253, 1212; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.20 – 7.18 (2 H, m, H<sub>4</sub>), 7.15 – 7.13 (2 H, m, H<sub>5</sub>), 3.59 (1 H, qt,  $J = 7.1$  Hz, H<sub>1</sub>), 3.17 (2 H, dd,  $J = 15.5, 7.2$  Hz, H<sub>2a</sub>), 2.75 (2 H, dd,  $J = 15.5, 6.9$  Hz, H<sub>2b</sub>), 2.42 (2 H, s, H<sub>6</sub>), 0.93 (9 H, s, H<sub>8</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : 142.2 (C<sub>3</sub>), 126.4 (C<sub>5</sub>), 124.8 (C<sub>4</sub>), 60.8 (C<sub>6</sub>), 60.6 (C<sub>1</sub>), 40.3 (C<sub>2</sub>), 31.5 (C<sub>7</sub>), 28.0 (C<sub>8</sub>);  $m/z$  HRMS found  $[M + H]^+$  204.1741, C<sub>14</sub>H<sub>22</sub>N requires 204.1747.

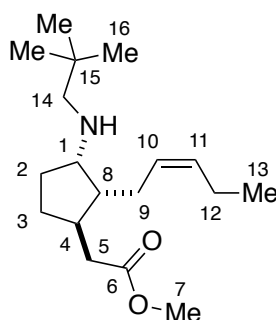
*N*-neopentylcyclohexanamine **539c**

General procedure D was applied to cyclohexanone (1.47 g, 15 mmol) and neopentylamine (1.31 g, 15 mmol) in dichloromethane (60 mL). The mixture was left to stir at room temperature for 72 hours. Purification by kugelrohr (90 °C, 10 mbar) gave the desired product as a colourless liquid (1.37 g, 54%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2928, 2854, 1465, 1449, 1394, 1361, 1289, 1257, 1214;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.35 (2 H, s,  $\text{H}_6$ ), 2.32 (1 H, tt,  $J = 10.4, 3.3$  Hz,  $\text{H}_1$ ), 1.86 – 1.84 (2 H, m,  $\text{H}_{2a}$ ), 1.71 (2 H, dt,  $J = 4.2, 12.8$  Hz,  $\text{H}_{3a}$ ), 1.61 – 1.58 (1 H, m,  $\text{H}_{4a}$ ), 1.28 – 1.02 (5 H, m,  $\text{H}_{2b}$ ,  $\text{H}_{3b}$  and  $\text{H}_{4b}$ ), 0.89 (9 H, s,  $\text{H}_8$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 59.8 ( $\text{C}_6$ ), 58.0 ( $\text{C}_1$ ), 33.9 ( $\text{C}_2$ ), 31.4 ( $\text{C}_7$ ), 28.0 ( $\text{C}_8$ ), 26.4 ( $\text{C}_4$ ), 25.3 ( $\text{C}_3$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  170.1902,  $\text{C}_{14}\text{H}_{24}\text{N}$  requires 170.1903.

*N*-neopentylcyclobutanamine **539d**

General procedure D was applied to cyclobutanone (1.75 g, 25 mmol) and neopentylamine (2.18 g, 25 mmol) in dichloromethane (100 mL). The mixture was left to stir at room temperature for 72 hours. The solvent was removed carefully by rotary evaporation (30 °C, 465 mbar). Subsequent purification by kugelrohr (60 °C, 50 mbar) gave the desired product as a colourless liquid (1.01 g, 29%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2953, 2866, 2811, 1464, 1395, 1362, 1337;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.19 (1 H, qt,  $J = 7.4$  Hz,  $\text{H}_1$ ), 2.24 – 2.19 (4 H, m,  $\text{H}_4$  and  $\text{H}_{2a}$ ), 1.68 – 1.57 (4 H, m,  $\text{H}_3$  and  $\text{H}_{2b}$ ), 0.89 (9 H, s,  $\text{H}_6$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 59.1 ( $\text{C}_4$ ), 54.8 ( $\text{C}_1$ ), 31.2 ( $\text{C}_2$ ), 30.9 ( $\text{C}_5$ ), 27.8 ( $\text{C}_6$ ), 14.6 ( $\text{C}_3$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  142.1586,  $\text{C}_9\text{H}_{20}\text{N}$  requires 142.1590.

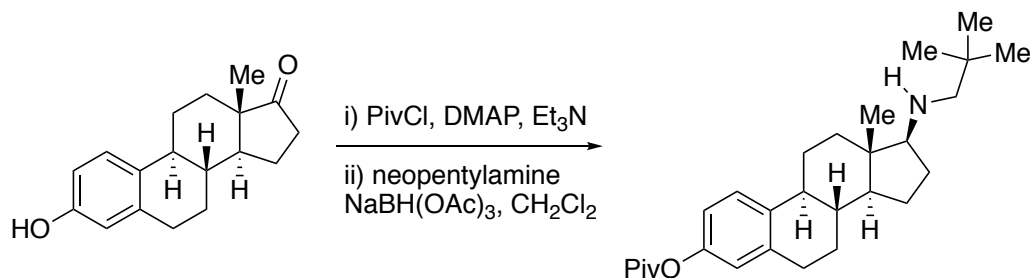
*methyl 2-(3-neopentylamino-2-((Z)-pent-2-en-1-yl)cyclopentyl)acetate* **539f**



General procedure D was applied to methyl jasmonate (2.18 mL, 10 mmol) and neopentylamine (1.18 mL, 10 mmol) in dichloromethane (50 mL). The mixture was left to stir at room temperature for 24 hours. The solvent was removed *in vacuo* and the crude oil purified by flash column chromatography (80:10:10 petroleum ether:ethyl acetate:dichloromethane) to afford the product as a colourless oil (0.95 g, 32%).  $R_f$  (80:10:10 petroleum ether:ethyl acetate:dichloromethane): 0.17; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2951, 2866, 1739, 1464, 1436, 1362, 1336, 1255, 1198, 1158;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.43 – 5.31 (2 H, m,  $\text{H}_{10}$  and  $\text{H}_{11}$ ), 3.65 (3 H, s,  $\text{H}_7$ ), 3.00 (1 H, q,  $J = 5.9$  Hz,  $\text{H}_1$ ), 2.46 (1 H, q,  $J = 9.3$  Hz,  $\text{H}_{5a}$ ), 2.31 (1 H, d,  $J = 10.9$  Hz,  $\text{H}_{14a}$ ), 2.21 – 2.11 (4 H, m,  $\text{H}_4$ ,  $\text{H}_{5b}$ ,  $\text{H}_{9a}$  and  $\text{H}_{14b}$ ), 2.10 – 1.95 (4 H, m,  $\text{H}_{3a}$ ,  $\text{H}_{9b}$  and  $\text{H}_{12}$ ), 1.75 – 1.67 (1 H, m,  $\text{H}_{2a}$ ), 1.60 – 1.46 (2 H, m,  $\text{H}_{2b}$  and  $\text{H}_8$ ), 1.27 – 1.18 (1 H, m,  $\text{H}_{3b}$ ), 0.96 (3 H, t,  $J = 7.4$  Hz,  $\text{H}_{13}$ ), 0.88 (9 H, s,  $\text{H}_{16}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 173.9 ( $\text{C}_6$ ), 132.5 ( $\text{C}_{11}$ ), 128.0 ( $\text{C}_{10}$ ), 61.3 ( $\text{C}_1$ ), 60.8 ( $\text{C}_{14}$ ), 51.5 ( $\text{C}_7$ ), 48.8 ( $\text{C}_8$ ), 40.6 ( $\text{C}_5$ ), 39.3 ( $\text{C}_4$ ), 31.7 ( $\text{C}_{15}$ ), 30.5 ( $\text{C}_2$ ), 29.2 ( $\text{C}_3$ ), 27.9 ( $\text{C}_{16}$ ), 25.8 ( $\text{C}_9$ ), 20.8 ( $\text{C}_{12}$ ), 14.4 ( $\text{C}_{13}$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  296.2581,  $\text{C}_{18}\text{H}_{34}\text{NO}_2$  requires 296.2584.



(8*R*,9*S*,13*S*,14*S*,17*S*)-13-methyl-17-(neopentylamino)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl pivalate **539g**



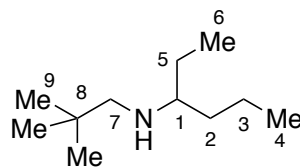
### Step 1

To a solution of estrone (0.95 g, 3.5 mmol) and 4-dimethylaminopyridine (4.3 mg, 0.035 mmol) in anhydrous dichloromethane (20 mL) was added triethylamine (0.44 g, 4.3 mmol) and the solution cooled to 0 °C. Pivaloyl chloride (0.52 g, 4.3 mmol) was added dropwise to the solution over 15 minutes and the reaction mixture was left to warm to room temperature over 12 hours. The reaction mixture was then washed with water (2 x 25 mL), 0.1 M HCl (25 mL), saturated aqueous NaHCO<sub>3</sub> (25 mL) and brine (25 mL). The organics were then dried over Na<sub>2</sub>SO<sub>4</sub> and removed *in vacuo* to afford the desired product as a white solid (1.17 g, 95%). The product was used in the next step without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.28 (d, *J* = 8.1 Hz), 6.82 (dd, *J* = 2.3, 8.4 Hz), 6.79 (d, *J* = 1.8 Hz), 2.91 – 2.89 (2 H, m), 2.51 (1 H, dd, *J* = 8.6, 19.0 Hz), 2.44 – 2.39 (1 H, m), 2.31 – 2.26 (1 H, m), 2.19 – 1.94 (4 H, m), 1.68 – 1.42 (6 H, m), 1.35 (9 H, s), 0.91 (3 H, s). Data consistent with literature<sup>635</sup>.

### Step 2

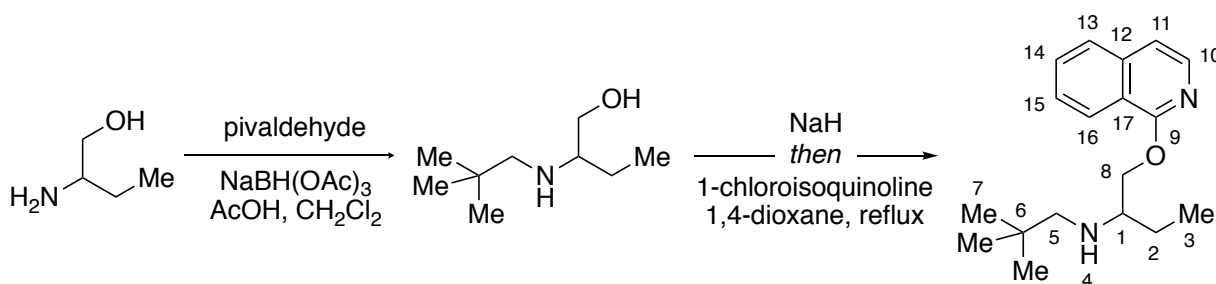
General procedure D was applied to estrone pivalate from Step 1 (1.17 g, 3.3 mmol) and neopentylamine (0.29 g, 3.3 mmol) in dichloromethane (30 mL). The mixture was left to stir at room temperature for 48 hours. Subsequent purification by flash column chromatography (80:10:10 hexane:ethyl acetate:dichloromethane) gave the desired product as a white solid (0.28 g, 20%). *R<sub>f</sub>* (80:10:10 hexane:ethyl acetate:dichloromethane): 0.16; IR *v*<sub>max</sub>/cm<sup>-1</sup> (film): 3345, 2950, 1746, 1641, 1540, 1494, 1478, 1395, 1363, 1278, 1211, 1154, 1125, 1030; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.24 (1 H, s), 6.78 (1 H, dd, *J* = 2.4, 8.2 Hz), 6.73 (1 H, d, *J* = 2.4 Hz), 5.65 (1 H, br s, N-H), 3.04 (1 H, dd, *J* = 6.72 Hz), 2.85 – 2.81 (2 H, m), 2.54 (1 H, t, *J* = 8.5 Hz), 2.36 (2 H, dd, *J* = 11.3, 20.1 Hz), 2.29 – 2.17 (2 H, m), 2.05 – 1.96 (2 H, m), 1.88 – 1.83 (1 H, m), 1.70 – 1.64 (1 H, m), 1.56 – 1.19 (16 H, m), 0.87 (9 H, s), 0.70 (3 H, s); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 177.5, 148.9, 138.4, 138.1, 126.4, 121.5, 118.5, 70.2, 61.4, 52.6, 50.5, 44.4, 43.4, 39.2, 38.7, 38.6, 31.9, 30.1, 29.7, 27.9, 27.4, 27.3 (2C), 26.6, 23.6, 11.9; HRMS found [M + H]<sup>+</sup> 426.3360, C<sub>28</sub>H<sub>44</sub>NO<sub>2</sub> requires 426.3367.

### *N*-neopentylhexan-3-amine **541a**



General procedure D was applied to 3-hexanone (2.50 g, 25 mmol) and neopentylamine (2.18 g, 25 mmol) in dichloromethane (100 mL). The mixture was left to stir at room temperature for 48 hours. Subsequent purification by kugelrohr (105 °C, 30 mbar) gave the desired product as a colourless liquid (2.90 g, 68%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2955, 2872, 1463, 1362;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.35 – 2.26 (3 H, m,  $\text{H}_1$  and  $\text{H}_7$ ), 1.42 – 1.32 (6 H, m,  $\text{H}_2$ ,  $\text{H}_3$  and  $\text{H}_5$ ), 0.92 – 0.85 (15 H, m,  $\text{H}_4$ ,  $\text{H}_6$  and  $\text{H}_9$ );  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$ : 59.4 ( $\text{C}_1$ ), 59.3 ( $\text{C}_7$ ), 36.2 ( $\text{C}_2$ ), 31.5 ( $\text{C}_8$ ), 27.8 ( $\text{C}_9$ ), 26.6 ( $\text{C}_5$ ), 19.2 ( $\text{C}_3$ ), 14.4 ( $\text{C}_4$ ), 10.0 ( $\text{C}_6$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  172.2056,  $\text{C}_{11}\text{H}_{26}\text{N}$  requires 172.2060.

### *1*-(isoquinolin-1-yloxy)-*N*-neopentylbutan-2-amine **543g**



#### Step 1

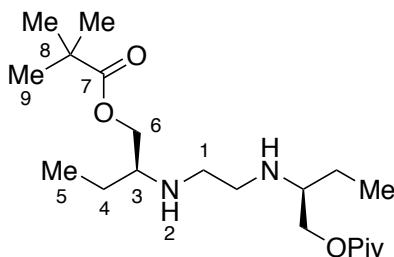
General procedure D was applied to 2-aminobutan-1-ol (4.7 mL, 50 mmol) and pivalaldehyde (5.4 mL, 50 mmol) in dichloromethane (200 mL). The mixture was left to stir at room temperature for 36 hours. After work up, the desired amine was obtained as a colourless oil (7.9 g, 99%). The product was used in the next step without further purification.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.59 (1H, dd,  $J$  = 10.6, 4.3 Hz), 3.23 (1H, dd,  $J$  = 10.6, 6.9 Hz), 3.16 (1H, br s), 2.50 (1H, m), 2.47 (1H, d,  $J$  = 11.4 Hz), 2.22 (1H, d,  $J$  = 11.4 Hz), 1.50 (1H, m), 1.39 (1H, m), 0.92 (9H, s), 0.91 (3H, t,  $J$  = 7.6 Hz), 0.68 (1H, br s);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 62.5, 60.9, 59.0, 31.6, 27.8, 24.7, 10.6.

#### Step 2

Sodium hydride (60% dispersion in mineral oil, 0.060 g, 2.5 mmol) was added portionwise to a solution of 2-(neopentylamino)butan-1-ol (0.40 g, 2.5 mmol) from Step 1 in anhydrous 1,4-dioxane (5 mL) and the mixture stirred at room temperature for 30 minutes. After such time, 1-

chloroisoquinoline (0.41 g, 2.5 mmol) was added and the mixture refluxed for 16 hours. Subsequently, the reaction was cooled to room temperature and concentrated *in vacuo*. The residue was added to water (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organics were washed with brine (30 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed *in vacuo* and purification by flash column chromatography (gradient elution: 100% petroleum ether to 10% ethyl acetate in petroleum ether) gave the desired amine as a pale yellow oil (0.44 g, 61%). *R<sub>f</sub>* (20% ethyl acetate in petroleum ether): 0.33; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3057, 2952, 1628, 1592, 1570, 1500, 1461, 1404, 1360, 1326; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.23 (1 H, d, *J* = 8.4 Hz, H<sub>16</sub>), 7.99 (1 H, d, *J* = 5.81 Hz, H<sub>10</sub>), 7.73 (1 H, d, *J* = 8.2 Hz, H<sub>13</sub>), 7.65 (1 H, dt, *J* = 1.1, 7.3 Hz, H<sub>15</sub>), 7.53 (1 H, dt, *J* = 1.1, 7.5 Hz, H<sub>14</sub>), 7.20 (1 H, d, *J* = 6.0 Hz, H<sub>11</sub>), 4.51 (dd, 1 H, *J* = 4.8, 11.0 Hz, H<sub>8a</sub>), 4.43 (dd, 1 H, *J* = 6.5, 10.2 Hz, H<sub>8b</sub>), 2.94 (1 H, qt, *J* = 5.6 Hz, H<sub>1</sub>), 2.50 (1 H, d, *J* = 11.4 Hz, H<sub>5a</sub>), 2.44 (1 H, d, *J* = 10.8 Hz, H<sub>5b</sub>), 1.70 – 1.60 (3 H, m, H<sub>2</sub> and H<sub>4</sub>), 1.03 (3 H, t, *J* = 7.5 Hz, H<sub>3</sub>), 0.92 (9 H, s, H<sub>7</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 160.7 (C<sub>9</sub>), 139.7 (C<sub>10</sub>), 137.9 (C<sub>17</sub>), 130.4 (C<sub>15</sub>), 126.6 (C<sub>14</sub>), 126.2 (C<sub>13</sub>), 124.0 (C<sub>16</sub>), 119.9 (C<sub>12</sub>), 114.9 (C<sub>11</sub>), 68.0 (C<sub>8</sub>), 59.5 (C<sub>5</sub>), 59.2 (C<sub>1</sub>), 31.6 (C<sub>6</sub>), 27.7 (C<sub>7</sub>), 24.9 (C<sub>2</sub>), 10.4 (C<sub>3</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 287.2113, C<sub>18</sub>H<sub>27</sub>ON<sub>2</sub> requires 287.2118.

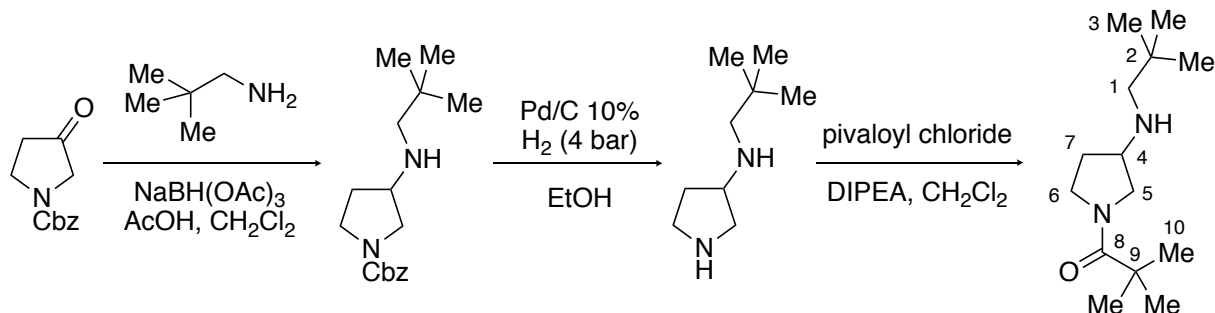
(2*S*,2'*S*)-(ethane-1,2-diylbis(azanediyl))bis(butane-2,1-diyl) bis(2,2-dimethylpropanoate) **543h**



To a solution of Ethambutol dihydrochloride (2.77 g, 10 mmol) in anhydrous dichloromethane (40 mL) was added triethylamine (6.14 mL, 44 mmol) and trimethylacetyl chloride (2.96 mL, 24 mmol) dropwise at 0 °C. The reaction mixture was warmed to room temperature over 16 hours and quenched by the addition of saturated aqueous NaHCO<sub>3</sub> (40 mL). The organic layer was separated and washed with additional saturated aqueous NaHCO<sub>3</sub> (2 x 40 mL), brine (40 mL) and dried over MgSO<sub>4</sub>. The solvent was removed *in vacuo* and the crude oil purified by flash column chromatography (gradient elution: 100% petroleum ether to 60% ethyl acetate in petroleum ether) to afford the product as a colourless oil (1.15 g, 31%). *R<sub>f</sub>* (80% ethyl acetate in petroleum ether): 0.13; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2962, 2877, 1728, 1480, 1461, 1398, 1365, 1282; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 4.06 (2 H, dd, *J* = 4.6, 10.9 Hz, H<sub>6a</sub>), 3.97 (2 H, dd, *J* = 4.6, 10.9 Hz, H<sub>6b</sub>), 2.77 – 2.63 (6 H, m, H<sub>1</sub> and H<sub>3</sub>), 1.61 (2 H, br s, H<sub>2</sub>), 1.46 (4 H, qt, *J* = 6.7 Hz, H<sub>4</sub>), 1.19 (18 H, s, H<sub>9</sub>), 0.92 (6 H, t, *J* = 7.7

Hz);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 178.6 ( $\text{C}_7$ ), 66.1 ( $\text{C}_6$ ), 58.0 ( $\text{C}_3$ ), 47.3 ( $\text{C}_1$ ), 39.0 ( $\text{C}_8$ ), 27.3 ( $\text{C}_9$ ), 24.9 ( $\text{C}_4$ ), 10.3 ( $\text{C}_5$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  373.3062,  $\text{C}_{20}\text{H}_{41}\text{N}_2\text{O}_4$  requires 373.3061.

### 1-pivaloyl-3-(neopentylamino)pyrrolidine **543i**



#### Step 1

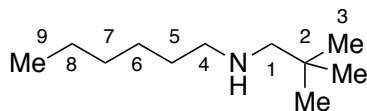
General procedure D was applied to *N*-benzyloxycarbonyl-3-pyrrolidinone (2.19 g, 10 mmol) and neopentylamine (0.87 g, 10 mmol) in dichloromethane (50 mL). The mixture was left to stir at room temperature for 48 hours. Subsequent purification by kugelrohr (165 °C, 0.75 mbar) gave *N*-benzyloxycarbonyl-3-(neopentylamino)pyrrolidine as a colourless oil (2.90 g, 54%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.39 – 7.30 (5 H, m), 5.14 (2 H, s), 3.64 – 3.51 (2 H, m), 3.45 – 3.38 (1 H, m), 3.33 – 3.25 (1 H, m), 3.14 (1 H, ddd,  $J$  = 5.5, 11.0, 26.1 Hz), 2.36 – 2.28 (2 H, m), 2.06 – 1.99 (1 H, m), 1.76 – 1.66 (1 H, m), 0.88 (9 H, s);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  155.0, 137.1, 128.4, 127.9, 127.8, 66.6, 60.5, 60.4, 58.5, 57.5, 52.4, 52.0, 44.7, 44.3, 32.1, 31.4, 31.3, 27.6.

#### Step 2

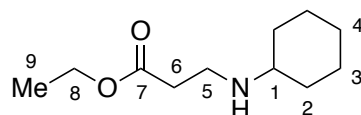
*N*-benzyloxycarbonyl-3-(neopentylamino)pyrrolidine from Step 1 (4.47 g, 15.4 mmol) was dissolved in absolute ethanol (30 mL) with 10% palladium on carbon (1.5 g). The mixture was subjected to Parr® hydrogenation at 4 bar hydrogen with stirring at room temperature for 4 hours. After such time, the mixture was filtered over celite and the solvent removed *in vacuo*. The residue was taken up in diethyl ether and filtered over a plug of activated charcoal. The solvent was removed *in vacuo* to give 3-(neopentylamino)pyrrolidine as a pale yellow liquid (1.90 g, 78%). The product was used in the next step without further purification.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.40 (1 H, br s, N-H), 3.36 – 3.32 (1 H, m), 3.28 – 3.22 (1 H, m), 3.15 – 3.04 (2 H, m), 2.92 (1 H, dd,  $J$  = 3.6, 11.5 Hz), 2.35 – 2.27 (2 H, m), 2.08 – 2.00 (1 H, m), 1.73 – 1.65 (1 H, m), 0.89 (9 H, s).

**Step 3**

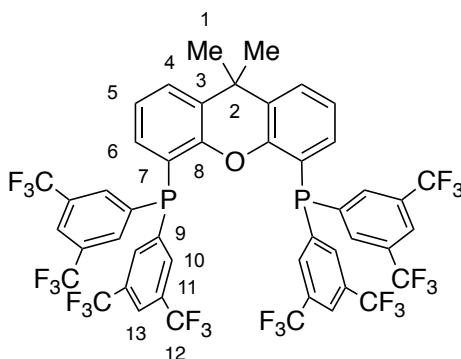
3-(neopentylamino)pyrrolidine from Step 2 (1.90 g, 12.1 mmol) was dissolved in anhydrous dichloromethane (40 mL) with diisopropylethylamine (1.56 g, 12.1 mmol). Pivaloyl chloride (1.46 g, 12.1 mmol) was added dropwise to the solution with stirring at room temperature. The mixture was left to stir for 3 hours and quenched with water (40 mL). The aqueous was extracted with dichloromethane (2 x 20 mL) and the combined organics were washed with sat. NaHCO<sub>3</sub>. The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent removed *in vacuo*. Purification by flash column chromatography (gradient elution: 30% ethyl acetate in petroleum ether to 60% ethyl acetate in petroleum ether) gave the desired amine as a pale yellow oil (1.12 g, 39%). *R<sub>f</sub>* (50% ethyl acetate in petroleum ether): 0.08; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3322, 2953, 2873, 1676, 1614, 1478, 1408, 1381, 1408; <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$ : 5.53 – 3.18 (4 H, br m, H<sub>5</sub>, H<sub>6</sub>), 2.77 (1 H, qt, *J* = 5.5 Hz, H<sub>4</sub>), 2.07 (2 H, s, H<sub>1</sub>), 1.51 – 1.43 (1 H, m, H<sub>7a</sub>), 1.27 – 1.16 (10 H, m, H<sub>7b</sub> and H<sub>10</sub>), 0.85 (9 H, s, H<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$ : 175.4 (C<sub>8</sub>), 60.4 (C<sub>1</sub>), 54.2 (br, C<sub>5</sub> or C<sub>6</sub>), 46.4 (br, C<sub>5</sub> or C<sub>6</sub>), 38.9 (C<sub>9</sub>), 31.5 (C<sub>2</sub>), 27.8 (C<sub>10</sub> or C<sub>3</sub>), 27.7 (C<sub>10</sub> or C<sub>3</sub>) [N.B. C<sub>4</sub> and C<sub>7</sub> could not be identified]; *m/z* HRMS found [M + H]<sup>+</sup> 241.2271, C<sub>14</sub>H<sub>29</sub>ON<sub>2</sub> requires 241.2274.

***N*-neopentylhexan-1-amine 547b**

General procedure D was applied to 1-hexylamine (2.53 g, 25 mmol) and pivaldehyde (2.15 g, 25 mmol) in dichloromethane (100 mL). The mixture was left to stir at room temperature for 72 hours. Purification by kugelrohr (83 °C, 20 mbar) gave the desired product as a colourless liquid (3.13 g, 73%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2954, 2928, 2860, 2808, 1464, 1379, 1362; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 2.58 (2 H, t, *J* = 7.6 Hz, H<sub>4</sub>), 2.33 (2 H, s, H<sub>1</sub>), 1.51 – 1.44 (2 H, m, H<sub>5</sub>), 1.31 – 1.27 (6 H, m, H<sub>6</sub>, H<sub>7</sub> and H<sub>8</sub>), 0.90 (9 H, s, H<sub>3</sub>), 0.88 (3 H, t, *J* = 6.8 Hz H<sub>9</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 62.7 (C<sub>1</sub>), 51.3 (C<sub>4</sub>), 32.0 (C<sub>6</sub>), 31.5 (C<sub>2</sub>), 30.2 (C<sub>5</sub>), 28.0 (C<sub>3</sub>), 27.8 (C<sub>7</sub>), 22.8 (C<sub>8</sub>), 14.2 (C<sub>9</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 172.2055, C<sub>11</sub>H<sub>26</sub>N requires 172.2060.

*ethyl 3-(cyclohexylamino)propanoate* **547c**

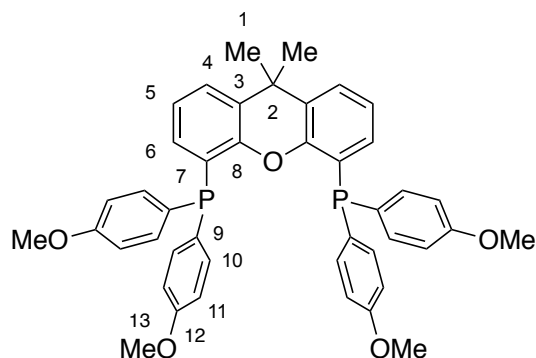
A solution of ethyl acrylate (1.50 g, 15 mmol) in absolute ethanol (7 mL) was added slowly dropwise to a solution of cyclohexylamine (2.98 g, 30 mmol) in absolute ethanol (20 mL) at 0 °C. The solution was warmed to room temperature over 16 hours and the solvent removed *in vacuo*. The resulting oil was purified by kugelrohr (170 °C, 45 mbar) to yield the desired compound as a colourless liquid (2.34 g, 78%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2925, 2853, 1732, 1449, 1371, 1348, 1301, 1174;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.13 (2 H, q,  $J = 7.0$  Hz,  $\text{H}_8$ ), 2.98 (2 H, t,  $J = 6.5$  Hz,  $\text{H}_5$ ), 2.49 (2 H, t,  $J = 6.5$  Hz,  $\text{H}_6$ ), 2.45 – 2.38 (1 H, m,  $\text{H}_1$ ), 1.88 – 1.85 (2 H, m,  $\text{H}_{2a}$ ), 1.74 – 1.70 (2 H, m,  $\text{H}_{3a}$ ), 1.62 – 1.59 (1 H, m,  $\text{H}_{4a}$ ), 1.30 – 1.00 (8 H, m,  $\text{H}_{2b}$ ,  $\text{H}_{3b}$ ,  $\text{H}_{4b}$  and  $\text{H}_9$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 172.9 ( $\text{C}_7$ ), 60.4 ( $\text{C}_8$ ), 56.5 ( $\text{C}_1$ ), 42.1 ( $\text{C}_5$ ), 35.1 ( $\text{C}_6$ ), 33.6 ( $\text{C}_2$ ), 26.2 ( $\text{C}_4$ ), 25.0 ( $\text{C}_3$ ), 14.2 ( $\text{C}_9$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  200.1641,  $\text{C}_{11}\text{H}_{22}\text{NO}_2$  requires 200.1645.

ii) *Synthesis of Ligands**4,5-bis(di(3,5-bis(trifluoromethyl)phenyl)phosphino)-9,9-dimethylxanthene* **511**

To a solution of xanthene (0.210 g, 1 mmol) and TMEDA (0.291 g, 2.5 mmol) in anhydrous hexane (5 mL) in an oven-dried Schlenk tube under Ar was added *n*-BuLi (2.0 M, 1.25 mL, 2.5 eq.) dropwise over 1 minute. The resulting solution was placed into a preheated oil bath at 85 °C and stirred for 50 minutes. After such time, the dark red solution was cooled to room temperature and subsequently to –78 °C (dry ice/acetone bath). A solution of bis(3,5-bis(trifluoromethyl)phenyl)chlorophosphine (1.25 g, 25 mmol) in anhydrous tetrahydrofuran (3 mL) was cooled separately to –78 °C (dry ice/acetone bath) and cannula transferred to the reaction mixture dropwise over 10 minutes with vigorous stirring. The resulting pale yellow solution was

allowed to warm to room temperature over 16 hours, then diluted with dichloromethane (50 mL). The solution was washed with water (2 x 25 mL), dried over  $\text{MgSO}_4$  and the solvent removed *in vacuo*. The residue was subjected to flash column chromatography (gradient elution: 100% hexane to 10% diethyl ether in hexane) and the crude product dissolved in the minimum amount of boiling methanol under  $\text{N}_2$ . The solution was cooled to room temperature and the solid collected by filtration to afford the product as an off-white powder (0.259 g, 23%) m.p. 152 – 154 °C; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 1615, 1411, 1354, 1275, 1251;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.88 (4 H, s,  $\text{H}_{13}$ ), 7.61 (8 H, s,  $\text{H}_{10}$ ), 7.57 (2 H, dd,  $J = 7.9, 1.3$  Hz,  $\text{H}_4$ ), 7.13 (2 H, t,  $J = 7.7$  Hz,  $\text{H}_5$ ), 6.40 (2 H, dq,  $J = 7.5, 1.9$  Hz,  $\text{H}_6$ ), 1.67 (6 H, s,  $\text{H}_1$ );  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  152.2 (t,  $^2J_{\text{C-P}} = 9.6$  Hz,  $\text{C}_8$ ), 138.9 – 138.8 (m,  $\text{C}_9$ ), 133.7 – 133.6 (m,  $\text{C}_{10}$ ), 132.3 (q,  $^2J_{\text{C-F}} = 33.7$  Hz,  $\text{C}_{11}$ ), 131.3 ( $\text{C}_3$ ), 131.2 ( $\text{C}_6$ ), 128.4 ( $\text{C}_4$ ), 126.3, 125.2 ( $\text{C}_5$ ), 123.6 ( $\text{C}_{13}$ ), 122.9 (q,  $^1J_{\text{C-F}} = 276.6$  Hz,  $\text{C}_{12}$ ), 121.4 – 121.3 (m,  $\text{C}_7$ ), 34.9 ( $\text{C}_2$ ), 31.2 ( $\text{C}_1$ );  $^{31}\text{P}\{^1\text{H}\}$  NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  -14.4;  $^{19}\text{F}\{^1\text{H}\}$  NMR (377 MHz,  $\text{CDCl}_3$ ) -63.1; m/z HRMS found  $[\text{M} + \text{H}]^+$  1123.1002,  $\text{C}_{47}\text{H}_{25}\text{F}_{24}\text{OP}_2$  requires 1123.0992. Data consistent with literature<sup>466</sup>.

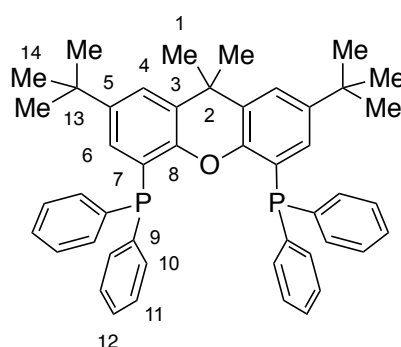
#### 4,5-bis(di(4-methoxy)phenyl)phosphino)-9,9-dimethylxanthene **512**



To a solution of xanthene (0.210 g, 1 mmol) and TMEDA (0.291 g, 2.5 mmol) in anhydrous hexane (5 mL) in an oven-dried Schlenk tube under Ar was added *n*-BuLi (2.0 M, 1.25 mL, 2.5 eq.) dropwise over 1 minute. The resulting solution was placed into a preheated oil bath at 85 °C and stirred for 50 minutes. After such time, the dark red solution was cooled to room temperature and subsequently to -78 °C (dry ice/acetone bath). A solution of bis(4-methoxyphenyl)chlorophosphine (0.72 g, 25 mmol) in anhydrous tetrahydrofuran (3 mL) was cooled separately to -78 °C (dry ice/acetone bath) and cannula transferred to the reaction mixture dropwise over 10 minutes with vigorous stirring. The resulting pale yellow solution was allowed to warm to room temperature over 16 hours, then diluted with dichloromethane (50 mL). The solution was washed with water (2 x 25 mL), dried over  $\text{MgSO}_4$  and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (gradient elution: 100% hexane to 20% ethyl acetate in hexane) to afford the

product as an off-white powder (0.319 g, 46%).  $R_f$  (20% ethyl acetate in petroleum ether): 0.40; m.p. 230 – 234 °C; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 1593, 1568, 1497, 1460, 1439, 1401, 1283, 1242;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37 (2 H, dd,  $J = 7.7, 1.3$  Hz,  $\text{H}_4$ ), 7.09 – 7.05 (8 H, m,  $\text{H}_{10}$ ), 6.94 (2 H, t,  $J = 7.6$  Hz,  $\text{H}_5$ ), 6.73 (8 H, d,  $J = 8.5$  Hz,  $\text{H}_{11}$ ), 6.52 (2 H, m,  $\text{H}_6$ ), 3.77 (12 H, s,  $\text{H}_{13}$ ), 1.63 (6 H, s,  $\text{H}_1$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  159.8 ( $\text{C}_{12}$ ), 152.6 ( $\text{C}_8$ ), 135.3 (t,  $^2J_{\text{C-P}} = 11.1$  Hz,  $\text{C}_{10}$ ), 132.0 ( $\text{C}_6$ ), 130.0 ( $\text{C}_3$ ), 128.7 (app t,  $^1J_{\text{C-P}} = 5.0$  Hz,  $\text{C}_9$ ), 127.0 – 128.8 (m,  $\text{C}_7$ ), 126.0 ( $\text{C}_4$ ), 123.4 ( $\text{C}_5$ ), 113.9 (t,  $^3J_{\text{C-P}} = 3.8$  Hz,  $\text{C}_{11}$ ), 55.1 ( $\text{C}_{13}$ ), 34.4 ( $\text{C}_2$ ) 31.9 ( $\text{C}_1$ );  $^{31}\text{P}\{^1\text{H}\}$  NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  –20.5; m/z HRMS found  $[\text{M} + \text{H}]^+$  699.2435,  $\text{C}_{43}\text{H}_{41}\text{O}_5\text{P}_2$  requires 699.2424. Data consistent with literature<sup>466</sup>.

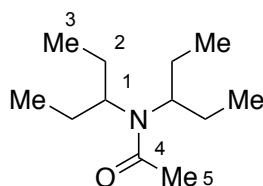
## 2, 7-di-tert-butylXantphos 508



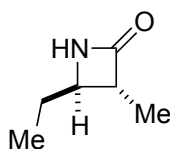
To a solution of 2,7-di-tert-butyl-4,5-dibromo-9,9-dimethylxanthene (0.480 g, 1 mmol) in anhydrous tetrahydrofuran (10 mL) in an oven-dried Schlenk flask at –78 °C (dry ice/acetone bath) under argon was added *n*-BuLi (2.5 M, 1 mL, 2.5 eq.) dropwise over 5 minutes with vigorous stirring. The pale yellow solution was allowed to stir at –78 °C for 1.5 hours after which time a solution of diphenylchlorophosphine (0.551 g, 2.5 mmol) in anhydrous tetrahydrofuran (2.5 mL) was added dropwise over 10 minutes. The resulting solution was allowed to warm to room temperature over 16 hours, during which time the solution became dark red/orange. The solution was diluted with dichloromethane (10 mL), washed with water (2 x 10 mL) and brine (10 mL), dried over  $\text{MgSO}_4$  and solvent removed *in vacuo*. The residue was purified twice by flash column chromatography (gradient elution: 100% hexane to 10% diethyl ether in hexane) to give the product as a white solid (0.322 g, 47%) m.p. 170 – 172 °C; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 3070, 2960, 2869, 1587, 1476, 1434, 1422, 1394, 1362, 1291, 1262, 1245, 1207;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.37 (2 H, d,  $J = 2.2$  Hz,  $\text{H}_4$ ), 7.25 – 7.20 (20 H, m,  $\text{H}_{10}$ ,  $\text{H}_{11}$  and  $\text{H}_{12}$ ), 6.52 (2 H, m,  $\text{H}_6$ ), 1.67 (6 H, s,  $\text{H}_1$ ), 1.10 (18 H, s,  $\text{H}_{14}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 150.6 (t,  $^2J_{\text{C-P}} = 8.7$  Hz,  $\text{C}_8$ ), 145.3 ( $\text{C}_5$ ), 137.8 (dd,  $J = 7.2, 6.4$  Hz), 134.0 (t,  $J = 10.4$  Hz) 129.5 ( $\text{C}_6$ ), 129.0 ( $\text{C}_3$ ), 128.2, 128.1 (t,  $J = 4.0$  Hz), 124.7 (dd,  $J = 8.0, 10.9$  Hz), 123.1 ( $\text{C}_4$ ), 34.6 ( $\text{C}_2$ ), 34.5 ( $\text{C}_{13}$ ), 32.3 ( $\text{C}_1$ ), 31.4 ( $\text{C}_{14}$ );  $^{31}\text{P}\{^1\text{H}\}$  (162 MHz,  $\text{CDCl}_3$ )  $\delta$ : –16.1; m/z HRMS found  $[\text{M} + \text{H}]^+$  691.3240,  $\text{C}_{47}\text{H}_{49}\text{OP}_2$  requires 691.3253. Data consistent with literature<sup>465</sup>.



## iii) Miscellaneous Procedures

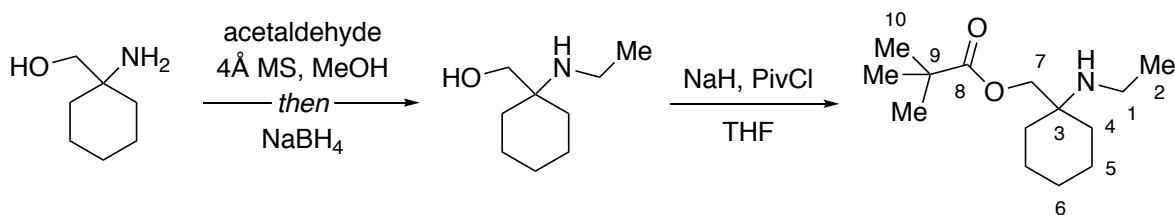
*N,N*-di(pentan-3-yl)acetamide **522**

To a solution of di(pentan-3-yl)amine (79 mg, 0.5 mmol) in anhydrous 1,2-dichloroethane (1 mL) was added montmorillonite K-10 powder (10 mg) and acetic anhydride (0.19 mL, 2.0 mmol) under  $N_2$ . The resulting solution was stirred at 50 °C for 24 hours. After such time, the solution was cooled to room temperature and the solid removed by filtration over celite. The solution was directly loaded onto silica gel and purified by flash column chromatography (gradient elution: 100% hexane to 10% isopropanol in hexane) to give the product as a colourless oil (64.0 mg, 64%). IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2966, 2936, 2877, 1635, 1431, 1377, 1361, 1344, 1312, 1266;  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 2.89 (1 H, br s,  $\text{H}_{1a}$ ), 2.27 (3 H, br s,  $\text{H}_{1b}$  and  $\text{H}_{2a}$ ), 1.91 – 1.87 (5 H, m,  $\text{H}_5$  and  $\text{H}_{2b}$ ), 1.24 – 1.19 (2 H, m,  $\text{H}_{2c}$ ), 1.11 (2 H, br s,  $\text{H}_{2d}$ ), 0.86 (6 H, t,  $J = 7.5$  Hz,  $\text{H}_{3a}$ ), 0.70 (6 H, t,  $J = 7.4$  Hz,  $\text{H}_{3b}$ ).  $^{13}\text{C}$  NMR (126 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 169.5 ( $\text{C}_4$ ), 63.0 ( $\text{C}_{1a}$ ), 59.1 ( $\text{C}_{1b}$ ), 27.0 ( $\text{C}_{2a}$ ), 26.5 ( $\text{C}_{2b}$ ), 23.8 ( $\text{C}_5$ ), 12.9 ( $\text{C}_{3a}$ ), 12.0 ( $\text{C}_{3b}$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  200.2005,  $\text{C}_{12}\text{H}_{26}\text{NO}$  requires 200.2009.

*cis*-4-ethyl-3-methylazetidin-2-one **552**

Liquid ammonia (*ca.* 10 mL) was condensed into a dry schlenk tube equipped with a cold-finger condenser cooled to  $-78$  °C. Sodium pellets (110 mg, 5 mmol) were added slowly portion-wise under a stream of  $N_2$  and the reaction mixture stirred at  $-78$  °C until complete dissolution had occurred, over which time the solution became dark blue. A solution of *trans*-1-(2,6-difluorobenzyl)-4-ethyl-3-methylazetidin-2-one **530d** in anhydrous tetrahydrofuran (110 mg, 0.5 mmol) was added slowly dropwise to the solution over 5 minutes and stirred at  $-78$  °C for an additional 10 minutes. After which time, powdered  $\text{NH}_4\text{Cl}$  (0.5 g) was added and the reaction mixture warmed to room temperature and excess ammonia removed *in vacuo*. The remaining residue was taken up in tetrahydrofuran (20 mL), filtered and the solvent removed *in vacuo*.  $^1\text{H}$  NMR analysis of the crude reaction mixture against an internal standard  $\text{Ph}_3\text{CH}$  indicated 63% yield of the desired lactam<sup>636</sup>.

## iv) Synthesis of Starting Amines for ATA C–H carbonylation

(1-(ethylamino)cyclohexyl)methyl pivalate **566****Step 1**

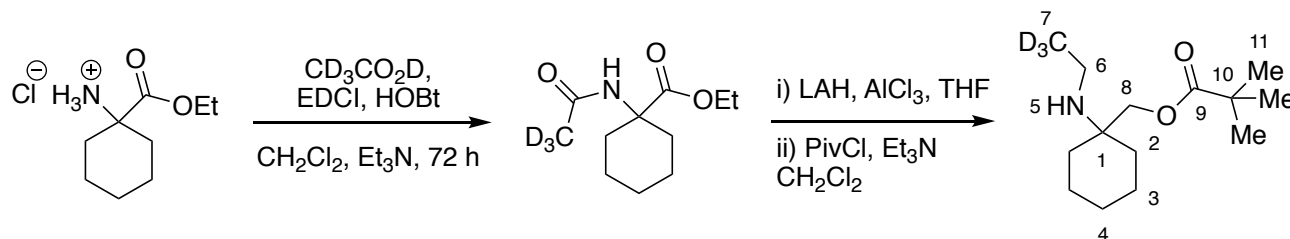
To a solution of (1-aminocyclohexyl)methanol (1.08 g, 8.4 mmol) in methanol (10 mL) was added powdered 4Å MS (1.0 g) and acetaldehyde (0.71 mL, 12.5 mmol) and the mixture stirred at ambient temperature for 16 h. The mixture was cooled to 0 °C, sodium borohydride (0.473 g, 12.5 mmol) was added portion-wise and the mixture allowed to warm to room temperature over 2 h. The reaction mixture was filtered and the methanol removed *in vacuo*. 10% Aqueous NaOH (10 mL) was added and the mixture extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried over MgSO<sub>4</sub> and concentrated *in vacuo* to afford the crude product as a white solid (1.12 g, 85%) which was used in the next step without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.29 (2 H, s), 2.50 (2 H, q, *J* = 7.1 Hz), 1.58 – 1.29 (10 H, m), 1.09 (3 H, t, *J* = 7.1 Hz).

**Step 2**

(1-(ethylamino)cyclohexyl)methanol (1.12 g, 7.12 mmol) was dissolved in tetrahydrofuran (15 mL) and cooled to 0 °C. Sodium hydride (60% in mineral oil, 0.29 g, 7.12 mmol) was added portion-wise and the reaction mixture stirred for 30 minutes at 0 °C. Trimethylacetyl chloride (1.05 mL, 8.55 mmol) was added drop-wise and the reaction mixture allowed to stir for 2 h at room temperature. The solution was concentrated *in vacuo* and water (15 mL) was added. The aqueous layer was extracted with dichloromethane (2 x 20 mL), the combined organic layers washed with saturated aqueous NaHCO<sub>3</sub> (15 mL) then water (15 mL), dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by flash column chromatography (alumina, gradient elution: 100% petroleum ether to 10% ethyl acetate in petroleum ether) to afford the title compound as a colourless oil (0.97 g, 57%). *R<sub>f</sub>* (20% ethyl acetate in petroleum ether): 0.10; IR ν<sub>max</sub>/cm<sup>-1</sup> (film): 2929, 2857, 1728, 1481, 1453, 1395, 1366, 1282, 115; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 3.95 (2 H, s, H<sub>7</sub>), 2.50 (2 H, q, *J* = 7.1 Hz, H<sub>1</sub>), 1.64 – 1.54 (2 H, m, H<sub>4a</sub>), 1.54 – 1.44 (3 H, m, H<sub>5a</sub> and H<sub>6a</sub>), 1.43 – 1.32 (5 H, m, H<sub>4b</sub>, H<sub>5b</sub> and H<sub>6b</sub>), 1.21 (9 H, s, H<sub>10</sub>), 1.06 (3 H, t, *J* = 7.1 Hz, H<sub>2</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ: 178.5 (C<sub>8</sub>),

67.5 (C<sub>7</sub>), 53.9 (C<sub>3</sub>), 39.1 (C<sub>9</sub>), 35.4 (C<sub>1</sub>), 33.0 (C<sub>4</sub>), 27.4 (C<sub>10</sub>), 26.2 (C<sub>6</sub>), 21.5 (C<sub>5</sub>), 16.3 (C<sub>2</sub>); m/z HRMS found [M + H]<sup>+</sup> 242.2108, C<sub>14</sub>H<sub>28</sub>NO<sub>2</sub> requires 242.2115.

*(1-((ethyl-2,2,2-d<sub>3</sub>)amino)cyclohexyl)methyl pivalate d<sub>3</sub>-566*



### Step 1

A solution of ethyl 1-aminocyclohexane-1-carboxylate hydrochloride (2.06 g, 10.0 mmol), *d*<sub>4</sub>-acetic acid (0.56 mL, 10.0 mmol), hydroxybenzotriazole (90%, 1.56 g, 15.0 mmol), EDCI hydrochloride (2.86 g, 15.0 mmol) and triethylamine (4.46 mL, 32.0 mmol) was stirred in dichloromethane (50 mL) for 72 hours. After such time the solution was washed with water (2 x 50 mL), sat. aqueous NaHCO<sub>3</sub> (2 x 50 mL), 1M HCl (2 x 50 mL) and brine (2 x 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent removed *in vacuo* to afford the product as a white solid (1.87 g, 86%) which was used without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 5.81 (1 H, br s, N-H), 4.13 (2 H, q, *J* = 7.2 Hz), 2.00 – 1.97 (2 H, m), 1.81 (2 H, td, *J* = 2.9, 11.7 Hz), 1.64 – 1.56 (3 H, m), 1.46 – 1.27 (3 H, m), 1.21 (3 H, t, *J* = 7.2 Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ: 174.2, 169.8, 61.1, 58.8, 32.4, 25.3, 22.7 (spt, *J* = 19.7 Hz), 21.6, 14.2; m/z HRMS found [M + H]<sup>+</sup> 217.1625, C<sub>11</sub>H<sub>16</sub>D<sub>3</sub>NO<sub>3</sub> requires 217.1626

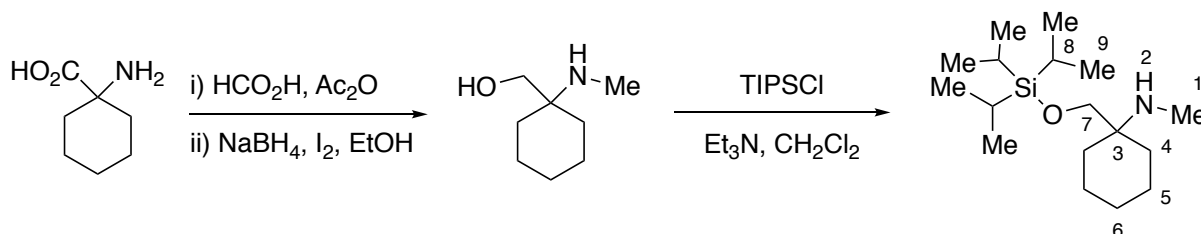
### Step 2

Aluminium trichloride (3.73 g, 28.0 mmol) was added carefully portionwise to anhydrous tetrahydrofuran (100 mL) in a 250 mL Schlenk flask at 0 °C under N<sub>2</sub>. Lithium aluminium hydride (3.19 g, 84 mmol) was subsequently added portionwise at 0 °C and allowed to stir at room temperature for 30 minutes. The amido ester (1.5 g, 7 mmol) was added as a solution in anhydrous tetrahydrofuran (10 mL) dropwise and allowed to stir at room temperature for 18 hours. The mixture was quenched by the dropwise addition of ethyl acetate (ca. 2 mL) and subsequently poured over crushed ice. The pH was adjusted to 3–4 using acetic acid and diluted with ethyl acetate (50 mL). The mixture was filtered over Celite and the organic layer separated. The aqueous was extracted using ethyl acetate (3 x 50 mL), the organics combined, washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the amino alcohol as a viscous oil (0.71 g, 63%) which was used without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.31 (2 H, s), 2.61 (2 H, br s), 2.50 (2 H, s), 1.56 – 1.28 (10 H, m); m/z HRMS found [M + H]<sup>+</sup> 161.1725, C<sub>9</sub>H<sub>17</sub>D<sub>3</sub>NO requires

161.1728.

**Step 3**

To a solution of crude amino alcohol (0.6 g, 3.7 mmol) in anhydrous dichloromethane (10 mL) was added triethylamine (0.77 mL, 5.6 mmol) and trimethylacetyl chloride (0.51 mL, 4.1 mmol) dropwise at 0 °C. The reaction mixture was warmed to room temperature over 16 hours and quenched by the addition of saturated aqueous NaHCO<sub>3</sub> (10 mL). The organic layer was separated and washed with additional saturated aqueous NaHCO<sub>3</sub> (2 x 10 mL), brine (10 mL) and dried over MgSO<sub>4</sub>. The solvent was removed *in vacuo* and the crude oil purified by flash column chromatography (gradient elution: 100% petroleum ether to 50% ethyl acetate in petroleum ether) to afford the product as a colourless oil (0.45 g, 50%). *R<sub>f</sub>* (20% ethyl acetate in petroleum ether): 0.11; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2931, 2856, 1730, 1480, 1460, 1397, 1364, 1282, 1151, 1053, 1034; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 3.98 (2 H, s, H<sub>8</sub>), 2.89 (1 H, br s, H<sub>5</sub>), 2.51 (2 H, s, H<sub>6</sub>), 1.62 – 1.35 (10 H, m, H<sub>2</sub>, H<sub>3</sub> and H<sub>4</sub>), 1.21 (9 H, s, H<sub>11</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 178.5 (C<sub>9</sub>), 67.0 (C<sub>8</sub>), 54.2 (C<sub>1</sub>), 39.1 (C<sub>10</sub>), 35.2 (C<sub>6</sub>), 32.8 (C<sub>2</sub>), 27.4 (C<sub>11</sub>), 26.1 (C<sub>4</sub>), 21.6 (C<sub>3</sub>), 15.2 (spt, *J* = 19.1 Hz, C<sub>7</sub>); <sup>2</sup>H NMR (77 MHz, CHCl<sub>3</sub> with 5% CDCl<sub>3</sub>)  $\delta$ : 1.05 (s); *m/z* HRMS found [M + H]<sup>+</sup> 245.2304, C<sub>14</sub>H<sub>25</sub>D<sub>3</sub>NO<sub>2</sub> requires 245.2303.

*N*-methyl-1-(((triisopropylsilyl)oxy)methyl)cyclohexan-1-amine **584c****Step 1**

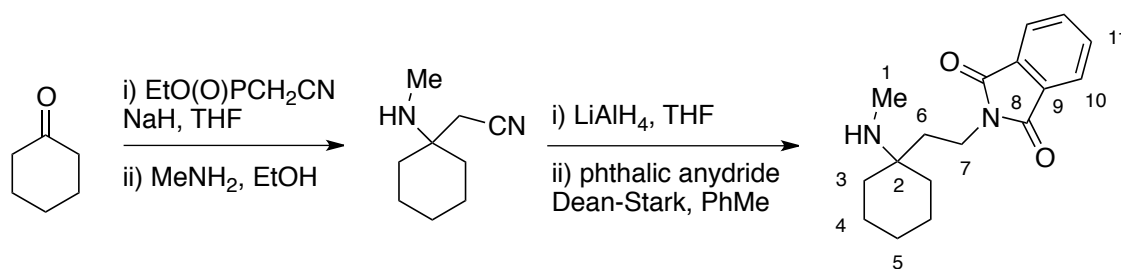
To a dry 250 mL 3-neck round-bottomed flask equipped with pressure-equalizing addition funnel, thermometer and nitrogen inlet was added 1-aminocyclohexane-1-carboxylic acid (7.16 g, 50 mmol) and formic acid (> 95%, 125 mL). Acetic anhydride (4.75 mL) was added dropwise over 30 minutes ensuring the temperature remained below 50 °C. The solution was stirred at room temperature for 90 minutes and was quenched with ice water (13 mL). The solvent was removed *in vacuo* to give the crude *N*-formyl amino acid which was used directly in the next step without further purification (quantitative yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 12.02 (1 H, br s), 7.94 (1 H, s), 1.99 – 1.88 (2 H, s), 1.70 – 1.58 (2 H, m), 1.56 – 1.39 (6 H, m).

**Step 2**

To a dry 250 mL 3-neck round-bottomed flask equipped with pressure-equalizing addition funnel and condenser under nitrogen was added *N*-formyl amino acid from Step 1 (6.84 g, 40 mmol), sodium borohydride (4.26 g, 112.2 mmol) and anhydrous tetrahydrofuran (100 mL). The mixture was cooled to 0 °C and a solution of iodine (11.85 g, 46.6 mmol) in anhydrous tetrahydrofuran (40 mL) was added dropwise with vigorous stirring (*Caution – vigorous gas evolution can be delayed!*). Once gas evolution had ceased the mixture was heated to a vigorous reflux for 18 hours. The mixture was cooled to room temperature and then to 0 °C and quenched cautiously by the dropwise addition of methanol. Once the solution had become clear, the solvent was removed *in vacuo* and the residue stirred with a mixture of 20% aqueous KOH (50 mL) and dichloromethane (50 mL) for 36 hours. The mixture was diluted with brine (100 mL) and dichloromethane (50 mL) and the organic layer separated. The aqueous was extracted with additional dichloromethane (3 x 50 mL), the organics were combined, dried over MgSO<sub>4</sub> and the solvent removed *in vacuo* to give the crude amino alcohol as a colourless oil (5.29 g, 92%) which was used in the next step without further purification. IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3304 (br), 2927, 2855, 1449, 1361, 1301, 1118, 1064, 1040; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 3.29 (2 H, s), 2.23 (3 H, s), 1.51 – 1.32 (10 H, m); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 64.7, 54.9, 32.1, 27.2, 26.1, 21.8; *m/z* HRMS found  $[M + H]^+$  144.1381, C<sub>8</sub>H<sub>18</sub>ON requires 144.1383.

**Step 3**

Triisopropylsilyl chloride (7.31 mL, 34.16 mmol) was added dropwise to a solution of amino alcohol from Step 2 (5.15 g, 36.0 mmol) and triethylamine (7.52 mL, 53.9 mmol) in anhydrous dichloromethane (100 mL) at 0 °C. The resulting solution was allowed to warm to room temperature over 16 hours and was quenched with water (100 mL). The organics were separated and washed with additional water (2 x 100 mL) and brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and removed *in vacuo*. The crude oil was purified by flash column chromatography (gradient elution: 1% methanol in dichloromethane to 5% methanol in dichloromethane) to provide the desired amine as pale yellow oil (5.56 g, 52%). *R<sub>f</sub>* (5% methanol in dichloromethane): 0.24; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2929, 2865, 1463, 1383, 1367, 1307, 1254, 1123, 1090, 1057; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 3.51 (2 H, s, H<sub>7</sub>), 2.25 (3 H, s, H<sub>1</sub>), 1.85 (1 H, br s, H<sub>2</sub>), 1.61 – 1.52 (2 H, m, H<sub>4a</sub>), 1.50 – 1.43 (3 H, m, H<sub>5a</sub> and H<sub>6a</sub>), 1.39 – 1.31 (5 H, m, H<sub>4b</sub>, H<sub>5b</sub> and H<sub>6b</sub>), 1.09 – 1.04 (21 H, m, H<sub>8</sub> and H<sub>9</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 65.8 (C<sub>7</sub>), 55.3 (C<sub>3</sub>), 32.0 (C<sub>4</sub>), 27.9 (C<sub>1</sub>), 26.4 (C<sub>6</sub>), 21.8 (C<sub>5</sub>), 18.2 (C<sub>9</sub>), 12.1 (C<sub>8</sub>); *m/z* HRMS found  $[M + H]^+$  300.2715, C<sub>17</sub>H<sub>38</sub>NOSi requires 300.2717.

*N*-(2-(1-(methylamino)cyclohexyl)ethyl)phthalimide **584h****Step 1**

Sodium hydride (60% in mineral oil, 1.20 g, 30 mmol) was added portionwise to a solution of diethyl cyanomethylphosphonate (4.85 mL, 30 mmol) in anhydrous tetrahydrofuran (20 mL) at 0 °C. The resulting slurry was allowed to stir at room temperature for 1 hour. The solution was cooled to 0 °C and a solution of cyclohexanone (2.07 mL, 20 mmol) in anhydrous tetrahydrofuran (5 mL) was added *via* syringe pump over 1 hour. The solution was allowed to warm to room temperature over 16 hours and was quenched with water (30 mL). The mixture was extracted with diethyl ether (3 x 40 mL) and the combined organics washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and removed *in vacuo*. The resulting oil was purified by kugelrohr (100 °C, 10 mbar) to give the product as a colourless oil (1.90 g, 78%); IR  $\nu_{\text{max}}$ /cm<sup>-1</sup> (film): 2936, 2859, 2216, 1632, 1449, 1344, 1325, 1268, 1134, 1026; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 5.03 (1 H, s), 2.48 (2 H, t, *J* = 6.4 Hz), 2.24 (2 H, t, *J* = 6.4 Hz), 1.70 – 1.57 (6 H, m); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : 168.8, 117.1, 92.1, 36.1, 33.3, 28.1, 27.7, 25.7; *m/z* HRMS found [M + H]<sup>+</sup> 122.0968, C<sub>8</sub>H<sub>12</sub>N requires 122.0970. Data consistent with literature<sup>637</sup>.

**Step 2**

A solution of 2-cyclohexylideneacetonitrile from Step 1 (1.89 g, 15.7 mmol) in ethanol (2 mL) and methylamine (33% w/w in EtOH, 3.9 mL, 31.3 mmol) were stirred at 80 °C in a sealed tube for 48 hours. After such time the solution was cooled to room temperature and the solvent removed *in vacuo*. The crude oil was purified by flash column chromatography (100% ethyl acetate) to provide the desired amine as a colourless oil (1.45 g, 61%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 2.43 (2 H, s), 2.29 (3 H, s), 1.66 – 1.23 (10 H, m), 1.18 (1 H, br s (N-H)). Data consistent with literature<sup>638</sup>.

**Step 3**

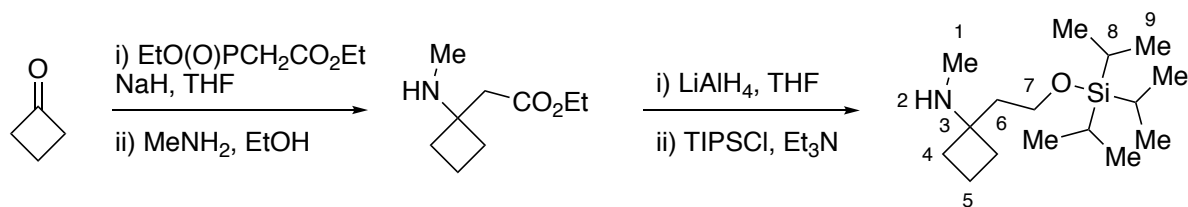
To a solution of ethyl 2-(1-(methylamino)cyclohexyl)acetonitrile from Step 2 (1.45 g, 9.5 mmol) in anhydrous diethyl ether (50 mL) was added lithium aluminium hydride (0.90 g, 23.8 mmol) portionwise at 0 °C and then heated at reflux for 16 hours. The resulting solution cooled to warm to

room temperature and was quenched successively with water (1 mL), 10% NaOH (1.3 mL) and water (2.5 mL). The resulting slurry was stirred with  $\text{MgSO}_4$  and filtered. The filter cake was washed with hot dichloromethane (100 mL). The filter cake was then removed and heated to 100 °C in 10% NaOH (100 mL) for 2 hours. The mixture was cooled to room temperature, filtered and the solution extracted with dichloromethane (3 x 100 mL). The combined organics were dried over  $\text{K}_2\text{CO}_3$  and removed *in vacuo* to afford the crude diamine as a colourless oil (1.16 g, 78%) which was used without further purification.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.72 (2 H, t,  $J = 8.0$  Hz), 2.26 (3 H, s), 1.54 – 1.41 (10 H, m), 1.37 – 1.29 (4 H, m).

#### Step 4

The crude diamine from Step 3 (1.16 g, 7.5 mmol), phthalic anhydride (1.10 g, 7.5 mmol) and triethylamine (1.04 mL, 7.5 mmol) were heated under Dean-Stark conditions in toluene (10 mL) for 6 hours. The solution was cooled to room temperature and the solvent removed *in vacuo* and the resulting oil purified by flash column chromatography (gradient elution: 1% methanol in dichloromethane to 5% methanol in dichloromethane) to provide the desired amine as a pale red viscous oil (1.53 g, 72%).  $R_f$  (5% methanol in dichloromethane): 0.25; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3351 (br), 2927, 2854, 2799, 1770, 1706, 1641, 1615, 1559, 1466, 1443, 1396, 1367, 1223, 1187, 1159, 1131;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.79 (2 H, dd,  $J = 3.1, 5.4$  Hz,  $\text{H}_{10}$ ), 7.66 (2 H, dd,  $J = 3.1, 5.4$  Hz,  $\text{H}_{11}$ ), 3.71 – 3.66 (2 H, m,  $\text{H}_7$ ), 2.32 (3 H, s,  $\text{H}_1$ ), 1.70 – 1.66 (2 H, m,  $\text{H}_6$ ), 1.52 – 1.32 (10 H, m,  $\text{H}_3$ ,  $\text{H}_4$  and  $\text{H}_5$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 168.5 ( $\text{C}_8$ ), 133.9 ( $\text{C}_{11}$ ), 132.4 ( $\text{C}_9$ ), 123.1 ( $\text{C}_{10}$ ), 53.1 ( $\text{C}_2$ ), 35.1 ( $\text{C}_3$ ), 34.2 ( $\text{C}_6$ ), 33.2 ( $\text{C}_7$ ), 27.5 ( $\text{C}_1$ ), 26.1 ( $\text{C}_4$ ), 21.7 ( $\text{C}_5$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  287.1754,  $\text{C}_{17}\text{H}_{23}\text{O}_2\text{N}_2$  requires 287.1754.

#### *N*-methyl-1-(2-((triisopropylsilyl)oxy)ethyl)cyclobutan-1-amine **584k**



#### Step 1

A solution of triethyl phosphonoacetate (19.8 g, 100 mmol) in anhydrous tetrahydrofuran (15 mL) was added dropwise *via* syringe pump to a suspension of sodium hydride (60% in mineral oil, 4.19 g, 104 mmol) in anhydrous tetrahydrofuran (120 mL) over 2 hours and the resulting solution was allowed to stir at room temperature for 30 minutes. After such time, a solution of cyclobutanone (7.4

mL, 100 mmol) in anhydrous tetrahydrofuran (6 mL) was added *via* syringe pump over 30 minutes and the resulting solution was allowed to stir at room temperature for 30 minutes. The reaction mixture was quenched by the addition of ice water (200 mL) and the resulting solution was extracted with diethyl ether (3 x 200 mL). The organics were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, and removed *in vacuo*. The resulting oil was purified by fractional distillation (75 °C, 13 mbar) to afford the product as a colourless oil (4.24 g, 30%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2917, 2849, 1713, 1673, 1466, 1394, 1367, 1335, 1264, 1244, 1222, 1185, 1086, 1039; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 5.56 (1 H, qt,  $J$  = 2.3 Hz), 4.12 (2 H, q,  $J$  = 7.0 Hz), 3.14 – 3.09 (2 H, m), 2.84 – 2.79 (2 H, m), 2.07 (2 H, qt,  $J$  = 8.0 Hz), 1.25 (3 H, t,  $J$  = 7.1 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : 167.7, 166.7, 112.5, 59.6, 33.8, 32.5, 17.8, 14.5;  $m/z$  HRMS found  $[M + H]^+$  141.0907, C<sub>8</sub>H<sub>13</sub>O<sub>2</sub> requires 141.0910. Data consistent with literature<sup>639</sup>.

## Step 2

A solution of ethyl 2-cyclobutylideneacetate from Step 1 (2.80 g, 20 mmol) and methylamine (33% w/w in EtOH, 4.98 mL, 40 mmol) were stirred at 80 °C in a sealed tube for 48 hours. After such time the solution was cooled to room temperature and the solvent removed *in vacuo* to afford the product as a colourless oil (3.13 g, 92%) which was used in the next step without further purification. IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3318 (br), 2938, 2797, 1727, 1660, 1559, 1446, 1368, 1317, 1245, 1206, 1177, 1149, 1058, 1030; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 4.10 (2 H, q,  $J$  = 7.1 Hz), 2.59 (2 H, s), 2.27 (3 H, s), 2.04 – 1.97 (2 H, m), 1.93 – 1.85 (2 H, m), 1.87 – 1.65 (3 H, m, (N-H)), 1.23 (3 H, t,  $J$  = 7.1 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : 172.0, 60.3, 58.7, 40.9, 31.5, 28.8, 14.4, 13.7;  $m/z$  HRMS found  $[M + H]^+$  172.1328, C<sub>9</sub>H<sub>18</sub>O<sub>2</sub>N requires 172.1332

## Step 3

To a solution of ethyl 2-(1-(methylamino)cyclobutyl)acetate (3.13 g, 18.3 mmol) in anhydrous tetrahydrofuran (60 mL) was added lithium aluminium hydride (1.39 g, 36.6 mmol) portionwise at 0 °C. The resulting solution was allowed to warm to room temperature over 16 hours and quenched successively with water (1.5 mL), 10% aqueous NaOH (2 mL) and water (4 mL). The resulting slurry was stirred with MgSO<sub>4</sub> and filtered. The filter cake was washed with diethyl ether (100 mL) and the combined organics removed *in vacuo* to afford the crude amino alcohol in quantitative yield, which was used without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 3.79 (2 H, t,  $J$  = 5.4 Hz), 2.28 (3 H, s), 1.97 – 1.67 (8 H, m).

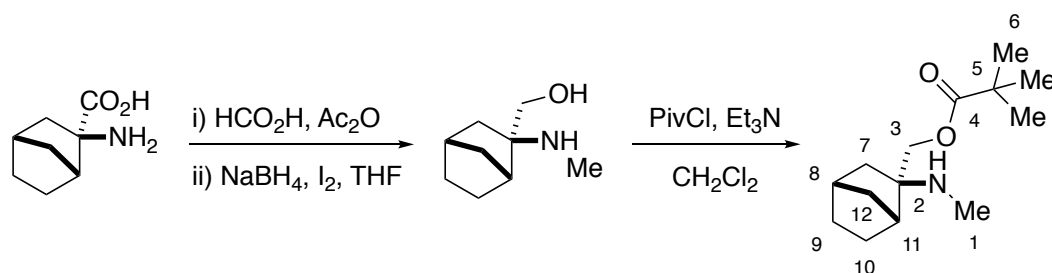
## Step 4

Triisopropylsilyl chloride (0.89 mL, 4.18 mmol) was added dropwise to a solution of amino alcohol



(0.56 g, 4.4 mmol) and triethylamine (0.92 mL, 6.6 mmol) in anhydrous dichloromethane (20 mL) at 0 °C. The resulting solution was allowed to warm to room temperature over 16 hours and was quenched with water (20 mL). The organics were separated and washed with additional water (2 x 20 mL) and brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and removed *in vacuo*. The crude oil was purified by flash column chromatography (gradient elution: 1% methanol in dichloromethane to 5% methanol in dichloromethane) to provide the desired amine as colourless oil (0.55 g, 44%). *R<sub>f</sub>* (5% methanol in dichloromethane): 0.12; IR  $\nu_{\text{max}}$ /cm<sup>-1</sup> (film): 2941, 2866, 1463, 1383, 1246, 1161, 1093, 1068, 1030; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 3.79 (2 H, t, *J* = 6.9 Hz, H<sub>7</sub>), 2.29 (3 H, s, H<sub>1</sub>), 2.0 – 1.94 (3 H, m, H<sub>4a</sub> and H<sub>2</sub>), 1.91 – 1.84 (4 H, H<sub>6</sub> and H<sub>4b</sub>), 1.80 – 1.68 (2 H, m, H<sub>5</sub>), 1.12 – 1.04 (21 H, m, H<sub>8</sub> and H<sub>9</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : 60.3 (C<sub>7</sub>), 59.5 (C<sub>3</sub>), 38.3 (C<sub>6</sub>), 31.9 (C<sub>4</sub>), 28.8 (C<sub>1</sub>), 18.2 (C<sub>9</sub>), 13.7 (C<sub>5</sub>), 12.1 (C<sub>8</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 286.2559, C<sub>16</sub>H<sub>36</sub>ONSi requires 286.2561.

*endo*-2-(methylamino)norbornane-2-methyl pivalate **584I**



**Step 1**

Acetic anhydride (2.94 mL, 31.1 mmol) was added dropwise to a solution of *endo*-2-amino-2-norbornanecarboxylic acid (0.65 g, 4.19 mmol) in formic acid (>95%, 8.7 mL) at 0 °C. The resulting solution was allowed to stir at room temperature for 1 hour and quenched with ice water (6 mL). The solvent was removed *in vacuo* to give the crude *N*-formyl amino acid (0.72 g) which was used directly in the next step without further purification. <sup>1</sup>H NMR (400 MHz, (CD<sub>3</sub>)<sub>2</sub>SO)  $\delta$ : 7.92 (1 H, s), 2.65 (1 H, d, *J* = 3.5 Hz), 2.17 – 2.10 (2 H, m), 2.07 (1 H, d, *J* = 10.0 Hz), 1.59 – 1.45 (2 H, m), 1.36 – 2.44 (3 H, m), 1.19 – 1.12 (1 H, m).

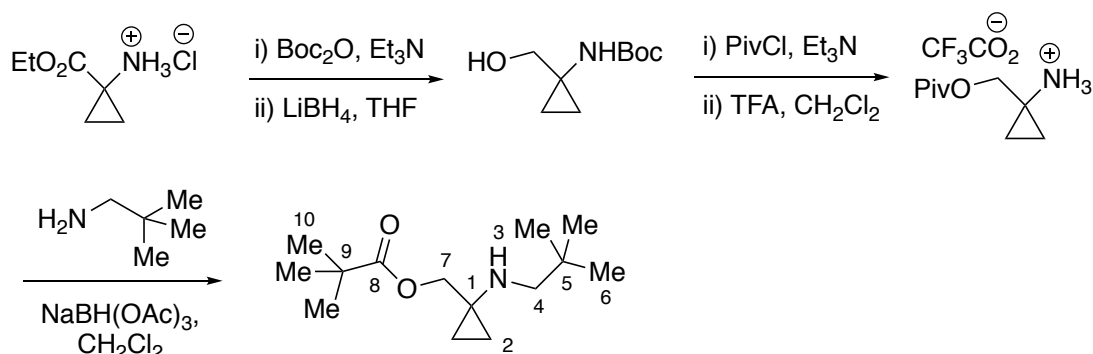
**Step 2**

To a vigorously stirred suspension of *N*-formyl amino acid from Step 1 (0.72 g, 3.9 mmol) and sodium borohydride (0.42 g, 11.1 mmol) in anhydrous tetrahydrofuran (10 mL) was added a solution of iodine (1.17 g, 4.6 mmol) in anhydrous tetrahydrofuran (5 mL) dropwise at 0 °C. Once gas evolution had ceased the mixture was heated at reflux for 18 hours and cooled to room temperature. Methanol was added cautiously until the solution became clear and the solvent was subsequently

removed *in vacuo* to afford a white paste. The paste was dissolved in the minimum amount of 20% aqueous KOH (ca. 4 mL) and stirred at room temperature for 1 hour. The mixture was diluted with 20% aqueous KOH (10 mL) and extracted with dichloromethane (3 x 15 mL). The organics were subsequently dried over Na<sub>2</sub>SO<sub>4</sub> and removed *in vacuo* to give the crude amino alcohol as a colourless oil (0.55 g, 91%) which was used in the next step without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.50 (1 H, d, *J* = 10.2 Hz), 3.24 (1 H, d, *J* = 10.5 Hz), 2.22 (3 H, s), 2.22 – 2.20 (1 H, m), 2.09 (1 H, d, *J* = 4.5 Hz), 1.68 (1 H, ddd, *J* = 3.1, 4.4, 13.0 Hz), 1.64 – 1.40 (3 H, m), 1.31 – 1.12 (3 H, m), 0.76 (1 H, dd, *J* = 2.7, 13.2 Hz).

### Step 3

To a solution of crude amino alcohol from Step 2 (0.55 g, 3.6 mmol) and 4-dimethylaminopyridine (22 mg, 0.18 mmol) in anhydrous dichloromethane (8 mL) was added trimethylacetyl chloride (0.52 mL, 4.3 mmol) dropwise. The reaction mixture was cooled to 0 °C and triethylamine (1.15 mL, 4.3 mmol) was added dropwise and the solution allowed to warm to room temperature over 16 h. The reaction was then diluted with dichloromethane (20 mL) and washed sequentially with water (2 x 30 mL), 0.1 M HCl (30 mL), sat. aqueous NaHCO<sub>3</sub> (30 mL) and brine (30 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (gradient elution: 5% ethyl acetate in petroleum ether to 100% ethyl acetate) to provide the desired amine as colourless oil (0.19 g, 20%). *R<sub>f</sub>* (20% ethyl acetate in petroleum ether): 0.08; IR *v*<sub>max</sub>/cm<sup>-1</sup> (film) 2950, 2870, 2800, 1727, 1480, 1467, 1443, 1397, 1364, 1328, 1313, 1282, 1152, 1101, 1064, 1036; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 4.12 (1 H, d, *J* = 11.4 Hz, H<sub>3a</sub>), 3.91 (1 H, d, *J* = 11.4 Hz, H<sub>3b</sub>), 2.25 (3 H, s, H<sub>1</sub>), 2.20 (1 H, app. t, *J* = 3.9 Hz, H<sub>11</sub>), 2.10 (1 H, app. d, *J* = 2.6 Hz, H<sub>8</sub>), 1.92 – 1.85 (1 H, m, H<sub>10a</sub>), 1.58 – 1.50 (2 H, m, H<sub>9a</sub> and H<sub>12a</sub>), 1.45 (1 H, ddd, *J* = 2.9, 4.4, 12.4 Hz, H<sub>7a</sub>), 1.37 – 1.24 (3 H, m, H<sub>9b</sub>, H<sub>10b</sub> and H<sub>12b</sub>), 1.21 (9 H, s, H<sub>6</sub>), 0.93 (1 H, dd, *J* = 2.9, 12.6 Hz, H<sub>7b</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ: 178.7 (C<sub>4</sub>), 65.3 (C<sub>3</sub>), 62.7 (C<sub>2</sub>), 42.1 (C<sub>8</sub>), 41.9 (C<sub>7</sub>), 39.1 (C<sub>5</sub>), 38.2 (C<sub>12</sub>), 36.9 (C<sub>11</sub>), 30.4 (C<sub>1</sub>), 29.0 (C<sub>9</sub>), 27.4 (C<sub>6</sub>), 22.8 (C<sub>10</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 240.1959, C<sub>14</sub>H<sub>26</sub>NO<sub>2</sub> requires 240.1958.

*(1-(neopentylamino)cyclopropyl)methyl pivalate* **584m****Step 1**

To a solution of ethyl 1-aminocyclopropane-1-carboxylate hydrochloride (3.22 g, 19.4 mmol) in anhydrous dichloromethane (35 mL) was added a solution of di-*tert*-butyl dicarbonate (4.24 g, 19.4 mmol) in anhydrous dichloromethane (5 mL) dropwise at room temperature. The solution was stirred at room temperature for 16 hours and quenched by the addition of aqueous potassium bisulfate (1 M, 100 mL) and additional dichloromethane (50 mL). The organic layer was separated, dried over  $\text{Na}_2\text{SO}_4$  and the solvent removed *in vacuo*. The residue was stripped with tetrahydrofuran (x 2) to afford the product as a viscous oil (3.96 g, 89%) which was used without further purification. IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3363, 2980, 2934, 1807, 1706, 1504, 1454, 1368, 1336, 1308, 1248, 1156, 1117, 1068, 1032;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.14 (1 H, br s), 4.12 (2 H, q,  $J = 7.3$  Hz), 1.51 – 1.45 (2 H, m), 1.43 (9 H, s), 1.22 (3 H, t,  $J = 7.0$  Hz), 1.15 – 1.10 (2 H, m);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 173.1, 156.1, 79.9, 61.2, 34.4, 28.3, 17.5, 14.2;  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  230.1387,  $\text{C}_{11}\text{H}_{20}\text{NO}_4$  requires 230.1387. Data consistent with literature<sup>640</sup>.

**Step 2**

To a stirred solution of ethyl 1-((*tert*-butoxycarbonyl)amino)cyclopropane-1-carboxylate from Step 1 (3.96 g, 17.3 mmol) in anhydrous tetrahydrofuran was added lithium borohydride (2.0 M in tetrahydrofuran, 17.3 mL, 34.5 mmol) dropwise at room temperature under  $\text{N}_2$ . The resulting solution was stirred at room temperature for 18 hours and was subsequently cooled to 0 °C. The reaction was quenched by the dropwise addition of 50% aqueous acetic acid, diluted with water (25 mL) and extracted with diethyl ether (50 mL). The organic layer was washed with 5% aqueous  $\text{NaHCO}_3$  (25 mL), brine (25 mL) and dried over  $\text{Na}_2\text{SO}_4$ . The solvent was removed *in vacuo* to afford the product as a white crystalline solid (2.41 g, 74%) which was used without further purification. IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3340, 3271, 2977, 2917, 1691, 1528, 1505, 1454, 1430, 1391, 1364, 1304, 1252, 1162, 1076, 1055, 1028, 1044;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.16 (1 H, br s), 3.59 (2 H, s), 1.45 (9 H, s), 0.83 (4 H, s);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 157.5, 80.2, 69.8, 35.2, 28.3, 12.8;

m/z HRMS found  $[M + H]^+$  188.1279,  $C_9H_{18}NO_3$  requires 188.1281. Data consistent with literature<sup>640</sup>.

### Step 3

To a solution of *tert*-butyl (1-(hydroxymethyl)cyclopropyl)carbamate from Step 2 (2.06 g, 11.0 mmol) and 4-dimethylaminopyridine (67 mg, 0.55 mmol) in anhydrous dichloromethane (25 mL) was added trimethylacetyl chloride (1.62 mL, 13.2 mmol) dropwise. The reaction mixture was cooled to 0 °C and triethylamine (1.84 mL, 13.2 mmol) was added dropwise and the solution allowed to warm to room temperature overnight. The reaction was then diluted with dichloromethane (50 mL) and washed sequentially with water (2 x 75 mL), 0.1 M HCl (75 mL), sat.  $NaHCO_3$  (75 mL) and brine (75 mL). The organic phase was dried over  $Na_2SO_4$  and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (gradient elution: 5% ethyl acetate in petroleum ether to 20% ethyl acetate) to provide the desired amine as colourless oil (2.08 g, 70%).  $R_f$  (10% ethyl acetate in petroleum ether): 0.26; IR  $\nu_{max}/cm^{-1}$  (film): 3366, 2977, 2935, 1704, 1505, 1481, 1457, 1393, 1366, 1280, 1246, 1149, 1075, 1033;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$ : 4.96 (1 H, br s), 4.11 (2 H, s), 1.45 (9 H, s), 1.23 (9 H, s), 0.87 – 0.81 (4 H, m);  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$ : 178.4, 155.4, 79.6, 68.4, 39.0, 32.6, 28.3, 27.2, 12.3; m/z HRMS found  $[M + H]^+$  272.1855,  $C_{14}H_{26}NO_4$  requires 272.1856.

### Step 4

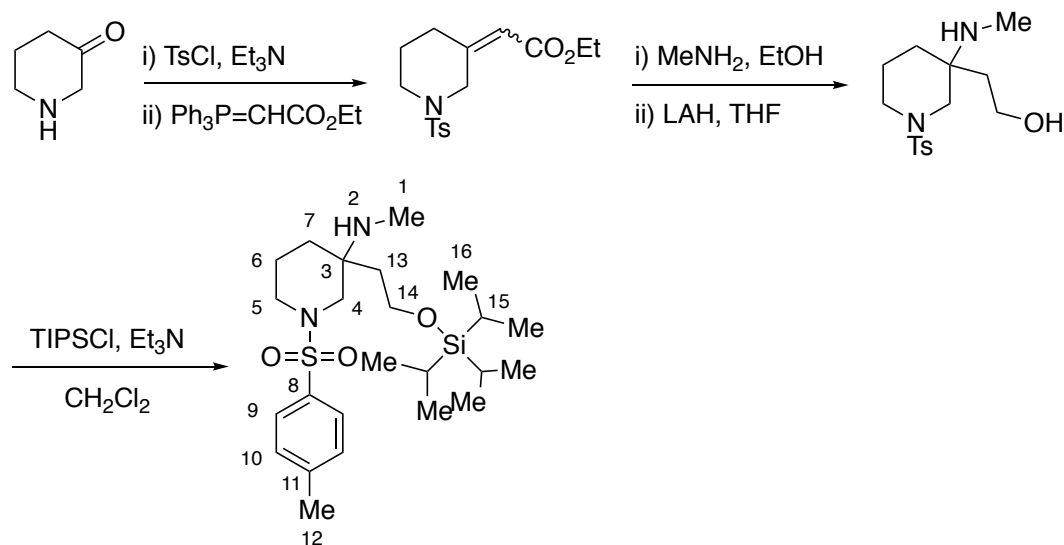
To a solution of (1-((*tert*-butoxycarbonyl)amino)cyclopropyl)methyl pivalate from Step 3 (1.90 g, 7.0 mmol) in anhydrous dichloromethane (15 mL) was added trifluoroacetic acid (3.6 mL) dropwise at 0 °C. The reaction mixture was warmed to room temperature over 16 hours and the solvent removed *in vacuo* and stored under hi-vac ( $>0.5$  mbar) to afford the product as a viscous oil (quantitative yield) which was used in the next step without further purification. IR  $\nu_{max}/cm^{-1}$  (film): 2975, 2910, 2876, 2628, 1723, 1674, 1591, 1544, 1479, 1430, 1316, 1282, 1139, 1034;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$ : 8.03 (3 H, br s), 4.23 (2 H, s), 1.28 (2 H, t,  $J = 7.6$  Hz), 1.24 (9 H, s), 1.00 (2 H, t,  $J = 7.6$  Hz);  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$ : 180.2, 161.4, (q,  $J = 39.5$  Hz), 115.2 (q,  $J = 285$  Hz), 67.9, 39.0, 35.4, 26.8, 10.0; m/z HRMS found  $[M + H]^+$  172.1327,  $C_9H_{18}NO_2$  requires 172.1332.

### Step 5

To a solution of 1-((pivaloyloxy)methyl)cyclopropylammonium trifluoroacetate from Step 4 (1.88 g, 6.6 mmol) in anhydrous tetrahydrofuran (40 mL) was added sodium bicarbonate (0.74 g, 8.8 mmol) and the mixture was allowed to stir at room temperature for 30 minutes. The reaction mixture was

subsequently cooled to 0 °C and trimethylacetaldehyde (0.84 mL, 7.6 mmol) and sodium triacetoxyborohydride (1.82 g, 8.6 mmol) were added sequentially. The reaction mixture was warmed to room temperature for 36 hours and quenched by the addition of 10% aqueous NaOH (50 mL). The mixture was stirred for 30 minutes and the layers were separated. The aqueous was extracted with dichloromethane (2 x 30 mL), the organics were combined and washed with brine (75 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed *in vacuo* and the crude oil was purified by flash column chromatography (gradient elution: 5% ethyl acetate in petroleum ether to 15% ethyl acetate) to provide the desired amine as colourless oil (0.98 g, 62%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.53; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2955, 2869, 1729, 1480, 1463, 1363, 1333, 1286, 1148, 1102; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 4.02 (2 H, s, H<sub>7</sub>), 2.40 (2 H, s, H<sub>4</sub>), 1.51 (1 H, br s, H<sub>3</sub>), 1.22 (9 H, s, H<sub>10</sub>), 0.84 (9 H, s, H<sub>6</sub>), 0.61 (2 H, dd, *J* = 4.7, 6.7 Hz, H<sub>2a</sub>), 0.51 (2 H, dd, *J* = 4.7, 6.7 Hz, H<sub>2b</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 178.7 (C<sub>8</sub>), 67.9 (C<sub>7</sub>), 58.3 (C<sub>4</sub>), 39.0 (C<sub>9</sub>), 38.4 (C<sub>1</sub>), 31.2 (C<sub>5</sub>), 27.6 (C<sub>6</sub>), 27.4 (C<sub>10</sub>), 12.6 (C<sub>2</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 242.2113, C<sub>14</sub>H<sub>28</sub>NO<sub>2</sub> requires 242.2115.

*N*-methyl-1-tosyl-3-(2-((triisopropylsilyl)oxy)ethyl)piperidin-3-amine **586a**



**Step 1**

Tosyl chloride (1.30 g, 6.8 mmol) was added portionwise to a solution of 3-piperidone hydrochloride hydrate (1 g, 6.5 mmol) and triethylamine (2.7 mL, 19.5 mmol) in dichloromethane (25 mL) at 0 °C. The solution was allowed to warm to room temperature over 16 hours and was quenched with water (20 mL). The organic layer was separated, and the aqueous extracted with additional dichloromethane (2 x 15 mL). The organics were combined and washed with 1M HCl (50 mL), brine (50 mL), dried over K<sub>2</sub>CO<sub>3</sub> and removed *in vacuo* to afford 1-tosyl-3-piperidone as a pale yellow solid which was used without further purification (1.37 g, 84%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2966, 2867,

1720, 1597, 1597, 1494, 1451, 1433, 1412, 1339, 1321, 1308, 1293, 1243, 1206, 1187;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.64 (2 H, d,  $J = 8.2$  Hz), 7.33 (2 H, d,  $J = 8.2$  Hz), 3.58 (2 H, s), 3.27 (2 H, t,  $J = 6.0$  Hz), 2.42 (3 H, s), 2.34 (2 H, t,  $J = 6.9$  Hz), 2.02 – 1.96 (2 H, m);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 202.7, 144.4, 132.8, 130.1, 127.8, 55.8, 44.6, 38.1, 22.8, 21.6;  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  284.0851,  $\text{C}_{12}\text{H}_{16}\text{NO}_3\text{S}$  requires 284.0851. Data consistent with literature<sup>641</sup>.

## Step 2

A solution of 1-tosyl-3-piperidone from Step 1 (2.30 g, 9.1 mmol) and ethyl (triphenylphosphoranylidene)acetate (3.48 g, 10 mmol) was refluxed in toluene (20 mL) for 24 hours. After such time the solution was cooled to room temperature and the solvent removed *in vacuo*. The resulting product was dissolved in ethyl acetate/petroleum ether (2:1, 50 mL), filtered over a pad of silica and celite, and washed with additional ethyl acetate/petroleum ether (2:1, 100 mL). The filtrate was collected and the solvent removed *in vacuo* and the resulting oil purified by flash column chromatography (gradient elution: 5% ethyl acetate in petroleum ether to 30% ethyl acetate in petroleum ether) to provide the desired products (1.97 g, 67%) as a mixture of diastereoisomers with *E*-form and *Z*-form (1:1).  $R_f$  (30% ethyl acetate in petroleum ether): 0.44, 0.5; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2929, 1712, 1657, 1598, 1445, 1381, 1349, 1305, 1268, 1152, 1105, 1090;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.69 – 7.63 (4 H, m), 7.33 – 7.29 (4 H, m), 5.77 (1 H, s), 5.68 (1 H, s), 4.28 (2 H, s), 4.21 – 4.11 (4 H, m), 3.54 (2 H, s), 3.20 (2 H, t,  $J = 5.0$  Hz), 3.13 (2 H, t,  $J = 4.90$ ), 2.79 (2 H, t,  $J = 5.6$  Hz), 2.43 (3 H, s), 2.42 (3 H, s), 2.21 (2 H, t,  $J = 5.6$  Hz), 1.78 – 1.70 (4 H, m), 1.31 – 1.25 (6 H, m);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 166.1, 165.7, 151.8, 151.7, 143.9, 143.6, 133.9, 133.2, 129.9, 129.8, 127.9, 127.8, 117.3, 116.8, 60.3, 60.2, 53.5, 46.8, 46.6, 46.0, 33.7, 26.9, 25.2, 24.9, 21.7, 21.6, 14.4, 14.3;  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  324.1264,  $\text{C}_{16}\text{H}_{22}\text{NO}_4\text{S}$  requires 324.1264.

## Step 3

A solution of ethyl 2-(1-tosylpiperidin-3-ylidene)acetate from Step 2 (1.97 g, 6.1 mmol) in ethanol (2 mL) and methylamine (33% w/w in EtOH, 1.5 mL, 12.2 mmol) were stirred at 80 °C in a sealed tube for 48 hours. After such time the solution was cooled to room temperature and the solvent removed *in vacuo*. The crude oil was purified by flash column chromatography (gradient elution: 1% methanol in dichloromethane to 5% methanol in dichloromethane) to provide the desired amine as colourless oil (1.52 g, 70%).  $R_f$  (5% methanol in dichloromethane): 0.30; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2942, 2855, 1725, 1598, 1493, 1466, 1446, 1339, 1305, 1269, 1246, 1215, 1159, 1091, 1056;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.60 (2 H, d,  $J = 8.4$  Hz), 7.29 (2 H, d,  $J = 8.1$  Hz), 4.11 (2 H, q,  $J = 7.1$  Hz),

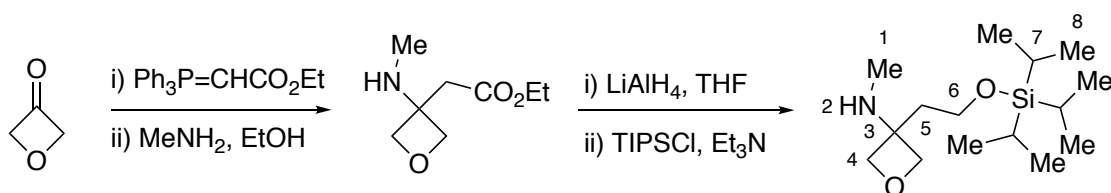
2.94 – 2.87 (4 H, m), 2.49 (2 H, s), 2.40 (3 H, s), 2.29 (3 H, s), 1.79 (1 H, br s, (N-H)), 1.72 – 1.62 (2 H, m), 152 – 1.41 (2 H, m), 1.24 (3 H, t,  $J = 7.1$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 171.2, 143.6, 133.2, 129.7, 127.7, 60.4, 53.8, 53.6, 46.6, 38.5, 32.3, 28.0, 21.6, 21.2, 14.3;  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  355.1685,  $\text{C}_{17}\text{H}_{27}\text{N}_2\text{O}_4\text{S}$  requires 355.1686.

#### Step 4

To a solution of ethyl 2-(3-(methylamino)-1-tosylpiperidin-3-yl)acetate from Step 3 (1.52 g, 4.3 mmol) in anhydrous tetrahydrofuran (30 mL) was added lithium aluminium hydride (0.65 g, 17.1 mmol) portionwise at 0 °C. The resulting solution was allowed to warm to room temperature over 6 hours and quenched successively with water (0.75 mL), 10% NaOH (1 mL) and water (2 mL). The resulting slurry was stirred with  $\text{MgSO}_4$  and filtered. The filter cake was washed with diethyl ether (100 mL) and the combined organics removed *in vacuo* to afford the crude amino alcohol (1.23 g, 91%) as a viscous oil, which solidified on standing and was used without further purification.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.63 (2 H, d,  $J = 8.3$  Hz), 7.33 (2 H, d,  $J = 7.8$  Hz), 3.80 – 3.74 (2 H, m), 3.56 – 3.51 (2 H, m), 2.44 (3 H, s), 2.35 (3 H, s), 2.19 (1 H, d,  $J = 11.2$  Hz), 1.86 – 1.48 (6 H, m), 1.22 – 1.13 (1 H, m).

#### Step 5

Triisopropylsilyl chloride (0.80 mL, 3.7 mmol) was added dropwise to a solution of amino alcohol from Step 4 (1.23 g, 3.9 mmol) and triethylamine (0.82 mL, 5.8 mmol) in anhydrous dichloromethane (15 mL) at 0 °C. The resulting solution was allowed to warm to room temperature over 16 hours and was quenched with water (20 mL). The organics were separated and washed with additional water (2 x 20 mL) and brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$  and removed *in vacuo*. The crude oil was purified by flash column chromatography (gradient elution: 50% ethyl acetate in petroleum ether to 100% ethyl acetate) to provide the desired amine as a white crystalline solid (1.49 g, 82%).  $R_f$  (ethyl acetate): 0.23; m.p. 76 – 77 °C; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3370, 2938, 2865, 2790, 1598, 1465, 1389, 1353, 1336, 1307, 1257, 1162, 1145, 1091, 1064;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.61 (2 H, d,  $J = 8.6$  Hz,  $\text{H}_9$ ), 7.30 (2 H, d,  $J = 8.2$  Hz,  $\text{H}_{10}$ ), 3.81 (2 H, t,  $J = 6.7$  Hz,  $\text{H}_{14}$ ), 3.27 – 3.24 (1 H, m,  $\text{H}_{5a}$ ), 3.19 (1 H, d,  $J = 11.5$  Hz,  $\text{H}_{4a}$ ), 2.58 – 2.53 (1 H, m,  $\text{H}_{5b}$ ), 2.50 (1 H, d,  $J = 11.5$  Hz,  $\text{H}_{4b}$ ), 2.42 (3 H, s,  $\text{H}_{12}$ ), 2.26 (3 H, s,  $\text{H}_1$ ), 1.74 (1 H, br s,  $\text{H}_2$ ), 1.71 – 1.55 (5 H, m,  $\text{H}_6$ ,  $\text{H}_{7a}$ , and  $\text{H}_{13}$ ), 1.32 – 1.25 (1 H, m,  $\text{H}_{7b}$ ), 1.06 – 1.02 (21 H, m,  $\text{H}_{15}$  and  $\text{H}_{16}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 143.5 ( $\text{C}_8$ ), 133.3 ( $\text{C}_{11}$ ), 129.7 ( $\text{C}_{10}$ ), 127.8 ( $\text{C}_9$ ), 59.2 ( $\text{C}_{14}$ ), 53.8 ( $\text{C}_4$ ), 52.9 ( $\text{C}_3$ ), 46.8 ( $\text{C}_5$ ), 37.1 ( $\text{C}_{13}$ ), 32.2 ( $\text{C}_7$ ), 27.9 ( $\text{C}_1$ ), 21.6 ( $\text{C}_{12}$ ), 21.2 ( $\text{C}_6$ ), 18.2 ( $\text{C}_{16}$ ), 12.0 ( $\text{C}_{15}$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  469.2904,  $\text{C}_{24}\text{H}_{45}\text{O}_3\text{N}_2\text{SSi}$  requires 469.2915.

*N*-methyl-3-(2-((triisopropylsilyl)oxy)ethyl)oxetan-3-amine **586b****Step 1**

Ethyl (triphenylphosphoranylidene)acetate (9.58 g, 27.5 mmol) was added portionwise to a solution of 3-oxetanone (1.46 mL, 25 mmol) in anhydrous dichloromethane (50 mL) at 0 °C. The resulting solution was warmed to room temperature over 15 minutes and solvent removed *in vacuo*. The resulting product was dissolved in petroleum ether/ethyl acetate (2:1, 50 mL), filtered over a pad of silica and celite, and washed with additional petroleum ether/ethyl acetate (2:1, 100 mL). The filtrate was collected and the solvent removed *in vacuo* to afford the product as a colourless oil (2.73 g, 71%) which was used without further purification. IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2984, 2926, 2859, 1718, 1694, 1446, 1371, 1344, 1297, 1251, 1265, 1201, 1098, 1035;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.61 (1 H, qt,  $J = 2.5$  Hz), 5.50 – 5.47 (2 H, m), 5.29 – 5.27 (2 H, m), 4.15 (2 H, q,  $J = 7.0$  Hz), 1.25 (3 H, t,  $J = 7.0$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 165.3, 159.3, 111.2, 81.2, 78.6, 60.5, 14.4;  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  143.0704,  $\text{C}_7\text{H}_{11}\text{O}_3$  requires 143.0708. Data consistent with literature<sup>523</sup>.

**Step 2**

A solution of ethyl 2-(oxetan-3-ylidene)acetate from Step 1 (2.73 g, 19.2 mmol) and methylamine (33% w/w in EtOH, 4.78 mL, 38.4 mmol) were stirred at 80 °C in a sealed tube for 36 hours. After such time the solution was cooled to room temperature and the solvent removed *in vacuo*. The crude oil was purified by flash column chromatography (ethyl acetate) to provide the desired amine as a colourless oil (1.49 g, 45%).  $R_f$  (ethyl acetate): 0.14; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3341, 2948, 2874, 2800, 1726, 1448, 1370, 1340, 1211, 1163, 1062, 1027;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.62 (2 H, d,  $J = 6.7$  Hz), 4.47 (2 H, d,  $J = 6.7$  Hz), 4.13 (2 H, t,  $J = 7.2$  Hz), 2.86 (2 H, s), 2.42 (3 H, s), 1.24 (3 H, t,  $J = 7.1$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 171.1, 80.0, 60.7, 59.0, 40.4, 29.5, 14.3;  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  174.1122,  $\text{C}_8\text{H}_{16}\text{O}_3\text{N}$  requires 174.1125

**Step 3**

To a solution of ethyl 2-(3-(methylamino)oxetan-3-yl)acetate from Step 2 (1.49 g, 8.6 mmol) in anhydrous diethyl ether (60 mL) was added lithium aluminium hydride (1.31 g, 34.4 mmol) portionwise at 0 °C. Approximately half way through the addition a thick precipitate formed which was dissolved by further addition of anhydrous tetrahydrofuran (20 mL) before the rest of the

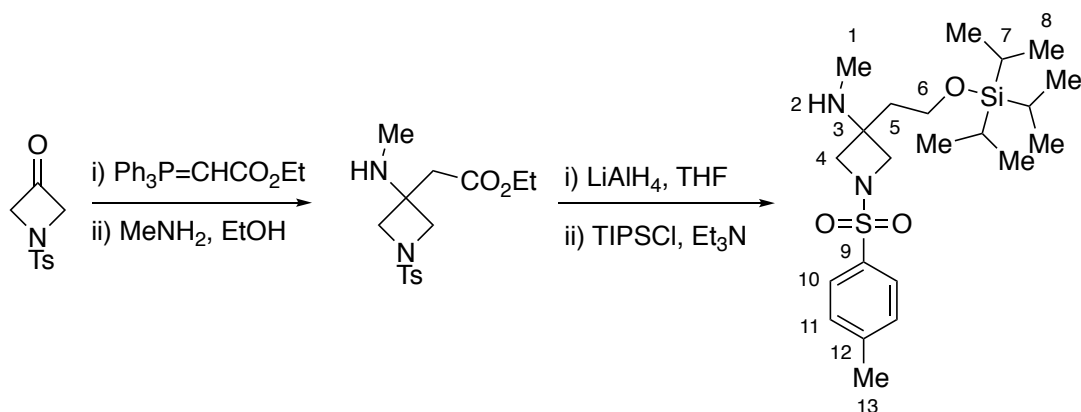


addition was continued. The resulting solution was allowed to warm to room temperature over 30 minutes and was quenched successively with water (1.5 mL), 10% NaOH (2 mL) and water (4 mL). The resulting slurry was stirred with MgSO<sub>4</sub> and filtered. The filter cake was washed with diethyl ether (100 mL) and the combined organics removed *in vacuo* to afford the crude amino alcohol (0.76 g, 67%) as a viscous oil and was used without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 4.53 (2 H, d, *J* = 6.7 Hz), 4.47 (2 H, d, *J* = 6.7 Hz), 3.77 (2 H, t, *J* = 5.5 Hz), 2.42 (3 H, s), 2.05 (2 H, t, *J* = 5.5 Hz).

#### Step 4

Triisopropylsilyl chloride (1.18 mL, 5.5 mmol) was added dropwise to a solution of amino alcohol from Step 3 (0.76 g, 5.8 mmol) and triethylamine (1.21 mL, 8.7 mmol) in anhydrous dichloromethane (20 mL) at 0 °C. The resulting solution was allowed to warm to room temperature over 16 hours and was quenched with water (20 mL). The organics were separated and washed with additional water (2 x 20 mL) and brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and removed *in vacuo*. The crude oil was purified by flash column chromatography (gradient elution: 5% ethyl acetate in petroleum ether to 100% ethyl acetate) to provide the desired amine as a colourless oil (0.80 g, 48%). *R<sub>f</sub>* (3:1 ethyl acetate in petroleum ether): 0.28; IR ν<sub>max</sub>/cm<sup>-1</sup> (film): 2942, 2866, 1463, 1383, 1267, 1248, 1169, 1098, 1069, 1012; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 4.58 (2 H, d, *J* = 6.4 Hz, H<sub>4a</sub>), 4.47 (2 H, d, *J* = 6.4 Hz, H<sub>4b</sub>), 3.81 (2 H, t, *J* = 6.2 Hz, H<sub>6</sub>), 2.41 (3 H, s, H<sub>1</sub>), 2.06 (2 H, d, *J* = 6.2 Hz, H<sub>5</sub>), 1.93 (1 H, br s, H<sub>2</sub>), 1.09 – 1.01 (21 H, m, H<sub>7</sub> and H<sub>8</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 80.7 (C<sub>4</sub>), 60.1 (C<sub>3</sub>), 59.8 (C<sub>6</sub>), 37.8 (C<sub>5</sub>), 29.3 (C<sub>1</sub>), 18.1 (C<sub>8</sub>), 12.0 (C<sub>7</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 441.2596, C<sub>22</sub>H<sub>41</sub>N<sub>2</sub>O<sub>3</sub>SSi requires 441.2602.

#### *N*-methyl-1-tosyl-3-(2-((triisopropylsilyl)oxy)ethyl)azetidin-3-amine **586c**



#### Step 1

Ethyl (triphenylphosphoranylidene)acetate (5.62 g, 16.5 mmol) was added portionwise to a solution

of 1-tosyl-3-azetidinone (3.55 g, 15 mmol) in anhydrous dichloromethane (30 mL) at 0 °C. The resulting solution was warmed to room temperature over 15 minutes and the solvent removed *in vacuo*. The resulting product was dissolved in ethyl acetate/petroleum ether (2:3, 50 mL), filtered over a pad of silica and celite, and washed with additional ethyl acetate/petroleum ether (2:3, 150 mL). The filtrate was combined and the solvent removed *in vacuo* to afford the product as a crystalline solid (1.63 g, 37%) which was used without further purification. IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2985, 1725, 1697, 1598, 1438, 1371, 1343, 1206, 1166, 1104;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.76 (2 H, d,  $J = 8.1$  Hz), 7.37 (2 H, d,  $J = 8.1$  Hz), 5.68 (1 H, qt,  $J = 2.2$  Hz), 4.73 (2 H, q,  $J = 2.8$  Hz), 4.50 (2 H, q,  $J = 2.4$  Hz), 4.13 (2 H, q,  $J = 7.1$  Hz), 2.45 (3 H, s), 1.24 (3 H, t,  $J = 7.1$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 165.0, 149.4, 144.6, 131.7, 130.1, 128.6, 114.7, 61.6, 60.7, 59.1, 21.8, 14.4;  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  296.0954,  $\text{C}_{14}\text{H}_{18}\text{NO}_4\text{S}$  requires 296.0951. Data consistent with literature<sup>642</sup>.

## Step 2

A solution of ethyl 2-(1-tosylazetidin-3-ylidene)acetate from Step 1 (1.63 g, 5.5 mmol) and methylamine (33% w/w in EtOH, 4.78 mL, 38.4 mmol) in ethanol (2 mL) were stirred at 80 °C in a sealed tube for 48 hours. After such time the solution was cooled to room temperature and the solvent removed *in vacuo*. The crude oil was purified by flash column chromatography (ethyl acetate) to provide the desired amine as a colourless oil (1.44 g, 80%).  $R_f$  (ethyl acetate): 0.14; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2978, 1728, 1598, 1439, 1371, 1343, 1163, 1119, 1093, 1043;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.74 (2 H, d,  $J = 8.3$  Hz), 7.73 (2 H, d,  $J = 8.0$  Hz), 4.10 (2 H, q,  $J = 7.1$  Hz), 3.70 (2 H, d,  $J = 8.6$  Hz), 3.63 (2 H, d,  $J = 8.6$  Hz), 2.63 (2 H, s), 2.45 (3 H, s), 2.12 (3 H, s), 1.23 (3 H, t,  $J = 7.2$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 170.7, 144.3, 131.7, 129.9, 128.5, 60.9, 58.7, 53.6, 41.0, 29.1, 21.7, 14.3;  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  327.1375,  $\text{C}_{15}\text{H}_{23}\text{N}_2\text{O}_4\text{S}$  requires 327.1373.

## Step 3

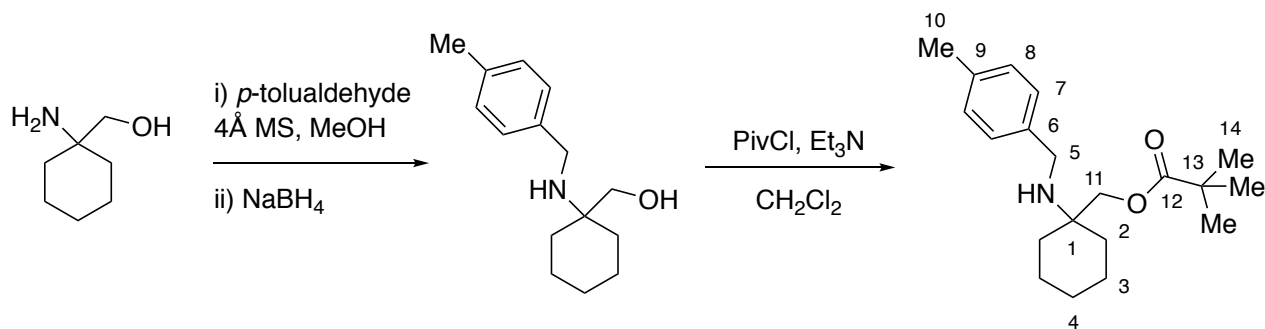
To a solution of ethyl 2-(3-(methylamino)-1-tosylazetidin-3-yl)acetate from Step 2 (1.44 g, 4.4 mmol) in anhydrous diethyl ether (25 mL) was added lithium aluminium hydride (0.67 g, 17.6 mmol) portionwise at 0 °C. Approximately three quarters through the addition a thick precipitate formed which was dissolved by the addition of anhydrous tetrahydrofuran (10 mL) before the rest of the addition was continued. The resulting solution was allowed to warm to room temperature over 2 hours and was quenched successively with water (1.5 mL), 10% NaOH (2 mL) and water (4 mL). The resulting slurry was stirred with  $\text{MgSO}_4$  and filtered. The filter cake was washed with hot dichloromethane (100 mL) and the combined organics removed *in vacuo* to afford the crude amino alcohol (0.97 g, 78%) as a white crystalline solid that was used without further purification (*Stench!*).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.73 (2 H, d,  $J = 8.4$  Hz), 7.37 (2 H, d,  $J = 8.4$  Hz), 3.66 (2 H, t,  $J = 5.4$  Hz), 3.60 (4 H, q,  $J = 8.4$  Hz), 2.46 (2 H, s), 2.21 (2 H, s), 1.75 (2 H, t,  $J = 5.3$  Hz).

#### Step 4

Triisopropylsilyl chloride (0.69 mL, 3.2 mmol) was added dropwise to a solution of amino alcohol from Step 3 (0.97 g, 3.4 mmol) and triethylamine (0.71 mL, 5.1 mmol) in anhydrous dichloromethane (10 mL) at 0 °C. The resulting solution was allowed to warm to room temperature over 16 hours and was quenched with water (10 mL). The organics were separated and washed with additional water (2 x 10 mL) and brine (10 mL), dried over  $\text{Na}_2\text{SO}_4$  and removed *in vacuo*. The crude oil was purified by flash column chromatography (gradient elution: 5% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether) to provide the desired amine as a colourless viscous oil (0.96 g, 64%).  $R_f$  (20% ethyl acetate in petroleum ether): 0.14; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2942, 2866, 1598, 1463, 1383, 1463, 1383, 1344, 1305, 1291, 1248, 1163, 1092, 1066;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.73 (2 H, d,  $J = 8.1$  Hz,  $\text{H}_{10}$ ), 7.36 (2 H, d,  $J = 8.1$  Hz,  $\text{H}_{11}$ ), 3.72 – 3.68 (4 H, m,  $\text{H}_6$  and  $\text{H}_{4a}$ ), 3.55 (2 H, d,  $J = 8.6$  Hz,  $\text{H}_{4b}$ ), 2.45 (3 H, s,  $\text{H}_{13}$ ), 2.11 (3 H, s,  $\text{H}_1$ ), 1.75 (2 H, t,  $J = 6.0$  Hz,  $\text{H}_5$ ), 1.66 (1 H, br s,  $\text{H}_2$ ), 1.03 – 0.98 (21 H, m,  $\text{H}_7$  and  $\text{H}_8$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 144.1 ( $\text{C}_9$ ), 131.7 ( $\text{C}_{12}$ ), 129.8 ( $\text{C}_{11}$ ), 128.5 ( $\text{C}_{10}$ ), 59.6 ( $\text{C}_6$ ), 59.2 ( $\text{C}_4$ ), 54.8 ( $\text{C}_3$ ), 38.6 ( $\text{C}_5$ ), 29.0 ( $\text{C}_1$ ), 21.7 ( $\text{C}_{13}$ ), 18.1 ( $\text{C}_8$ ), 11.9 ( $\text{C}_7$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  441.2596,  $\text{C}_{22}\text{H}_{41}\text{N}_2\text{O}_3\text{SSi}$  requires 441.2602.

#### (1-((4-methylbenzyl)amino)cyclohexyl)methyl pivalate **595a**



#### Step 1

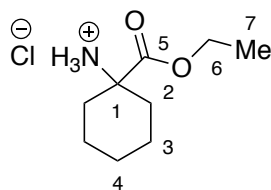
To a solution of (1-aminocyclohexyl)methanol (1.0 g, 7.7 mmol) and powdered 4Å MS (1.0 g) in anhydrous methanol (10 mL) was added *p*-tolualdehyde (1.36 mL, 11.6 mmol). The resulting mixture was stirred at room temperature for 16 hours and cooled to 0 °C. Sodium borohydride (0.44 g, 11.6 mmol) was cautiously added portionwise and the reaction mixture warmed to room temperature over 2 hours. The crude reaction mixture was filtered over celite, washed with methanol and the solvent removed *in vacuo*. The resulting white paste was dissolved in 10% aqueous NaOH

(30 mL) and stirred at room temperature for 2 hours. The aqueous was extracted with dichloromethane (3 x 30 mL) and concentrated *in vacuo*. The resulting product was dissolved in 3M HCl (30 mL) and water (30 mL), washed with diethyl ether (3 x 30 mL) and the resulting aqueous layer was cooled to 0 °C and basified carefully to pH = 10 with sodium hydroxide pellets. The solution was extracted with dichloromethane (3 x 30 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and removed *in vacuo* to afford the crude amino alcohol as a white solid (1.43 g, 79%), which was used without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.23 (2 H, d, *J* = 7.8 Hz), 7.14 (2 H, d, *J* = 7.8 Hz), 3.59 (2 H, s), 3.37 (2 H, s), 2.34 (3 H, s), 1.65 – 1.37 (10 H, m).

## Step 2

To a solution of crude amino alcohol from Step 1 (0.90 g, 3.9 mmol) in anhydrous dichloromethane (20 mL) was added triethylamine (1.19 mL, 8.6 mmol) and trimethylacetyl chloride (0.52 mL, 4.3 mmol) dropwise at 0 °C. The reaction mixture was warmed to room temperature over 16 hours and quenched by the addition of saturated aqueous NaHCO<sub>3</sub> (20 mL). The organic layer was separated and washed with additional saturated aqueous NaHCO<sub>3</sub> (2 x 20 mL), brine (20 mL) and dried over MgSO<sub>4</sub>. The solvent was removed *in vacuo* and the crude oil purified by flash column chromatography (gradient elution: 100% petroleum ether to 10% ethyl acetate in petroleum ether) to afford the product as a white solid (0.90 g, 73%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.38; m.p. 42 – 44 °C; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3321, 2923, 2848, 1712, 1514, 1481, 1463, 1441, 1398, 1360, 1286, 1185, 1166, 1088; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.24 (2 H, d, *J* = 7.7 Hz, H<sub>8</sub>), 7.12 (2 H, d, *J* = 7.7 Hz, H<sub>7</sub>), 4.03 (2 H, s, H<sub>5</sub>), 3.60 (2 H, s, H<sub>11</sub>), 2.33 (3 H, s, H<sub>10</sub>), 1.73 – 1.56 (5 H, m, H<sub>2a</sub>, H<sub>3a</sub> and H<sub>4a</sub>), 1.47 – 1.30 (5 H, m, H<sub>2b</sub>, H<sub>3b</sub> and H<sub>4b</sub>), 1.22 (9 H, s, H<sub>14</sub>). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ: 178.6 (C<sub>12</sub>), 138.5 (C<sub>6</sub>), 136.5 (C<sub>9</sub>), 129.2 (C<sub>8</sub>), 128.4 (C<sub>7</sub>), 68.1 (C<sub>11</sub>), 54.2 (C<sub>1</sub>), 45.6 (C<sub>5</sub>), 39.1 (C<sub>13</sub>), 32.9 (C<sub>2</sub>), 27.4 (C<sub>14</sub>), 26.3 (C<sub>4</sub>), 21.4 (C<sub>3</sub>), 21.2 (C<sub>10</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 318.2429, C<sub>20</sub>H<sub>32</sub>NO<sub>2</sub> requires 344.2428.

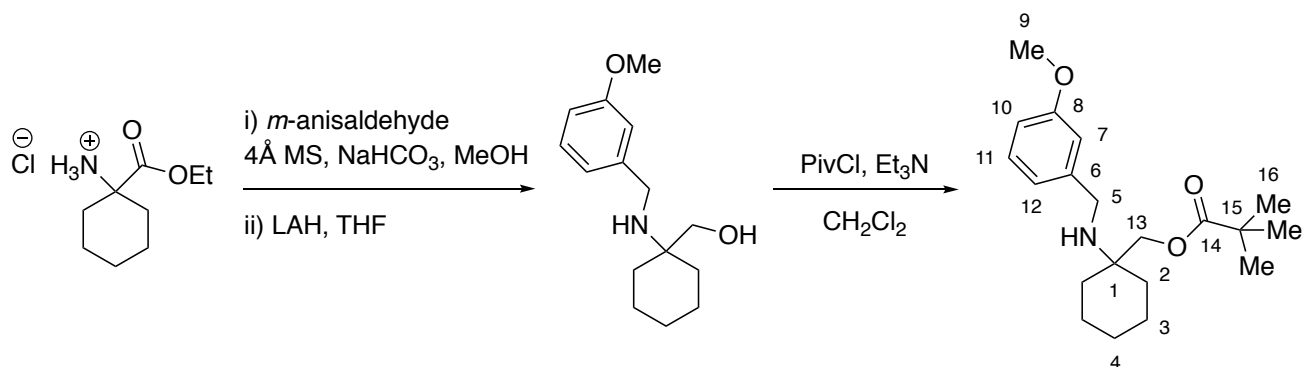
## Ethyl 1-aminocyclohexanecarboxylate hydrochloride **690**



Thionyl chloride (30 mL) was added dropwise to a suspension of 1-aminocyclohexane-1-carboxylic acid hydrochloride (8.95 g, 50 mmol) in absolute ethanol (200 mL) at 0 °C. The resulting mixture was heated to reflux for 16 hours and subsequently cooled to room temperature. The solvent was

removed *in vacuo* and residue dried under hi-vac (>1 mbar, 75 °C) to afford the product as a free-flowing white powder (10.2 g, 99%). M.p. 182 °C (sharp); IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2938, 2897, 2853, 1743, 1597, 1569, 1519, 1471, 1452, 1391, 1367, 1293, 1244, 1154, 1107, 1042, 1023;  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ )  $\delta$ : 4.32 (2 H, q,  $J = 7.1$  Hz,  $\text{H}_6$ ), 2.17 – 2.10 (2 H, m,  $\text{H}_{2a}$ ), 1.85 – 1.73 (4 H, m,  $\text{H}_{2b}$  and  $\text{H}_{3a}$ ), 1.60 – 1.50 (4 H, m,  $\text{H}_{3b}$  and  $\text{H}_4$ ), 1.32 (3 H, t,  $J = 7.1$  Hz,  $\text{H}_7$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{D}_2\text{O}$ )  $\delta$ : 172.2 ( $\text{C}_5$ ), 63.6 ( $\text{C}_6$ ), 59.9 ( $\text{C}_1$ ), 31.1 ( $\text{C}_2$ ), 23.5 ( $\text{C}_4$ ), 20.2 ( $\text{C}_3$ ), 13.1 ( $\text{C}_7$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  172.1328,  $\text{C}_9\text{H}_{18}\text{NO}_2$  requires 172.1332. Data consistent with literature<sup>643</sup>.

*(1-((3-methoxybenzyl)amino)cyclohexyl)methyl pivalate* **595b**



### Step 1

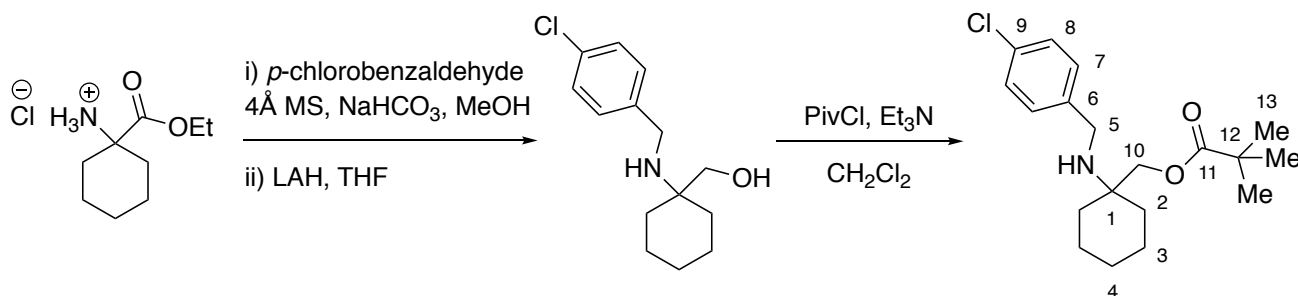
To a solution of ethyl 1-aminocyclohexanecarboxylate hydrochloride **690** (1.03 g, 5.0 mmol), sodium bicarbonate (0.42 g, 5.5 mmol) and powder 4Å MS (1.0 g) in anhydrous methanol (10 mL) was added *m*-anisaldehyde (0.61 mL, 5.0 mmol). The reaction was allowed to stir at room temperature for 16 hours and was subsequently filtered over celite and washed with methanol. The solvent was removed *in vacuo* and dried under vacuum. The resulting residue was dissolved in anhydrous tetrahydrofuran (25 mL) and cooled to 0 °C before lithium aluminium hydride (0.57 g, 15.0 mmol) was added portion-wise. The reaction mixture was warmed to room temperature over 2 hours, cooled to 0 °C and quenched successively with water (0.75 mL), 10% NaOH (1 mL) and water (2 mL). The resulting slurry was stirred with  $\text{MgSO}_4$  and filtered. The filter cake was washed with diethyl ether (100 mL) and the combined organics removed *in vacuo* to afford the crude amino alcohol as a colourless oil (1.25 g, 99%), which was used without further purification.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.25 (1 H, app t,  $J = 7.7$  Hz), 6.94 – 6.90 (2 H, m), 6.80 (1 H, ddd,  $J = 0.7, 2.6, 8.3$  Hz), 3.81 (3 H, s), 3.60 (2 H, s), 3.37 (2 H, s), 1.64 – 1.60 (2 H, m), 1.54 – 1.39 (8 H, m).

### Step 2

To a solution of crude amino alcohol (1.0 g, 4.0 mmol) in anhydrous dichloromethane (20 mL) was

added triethylamine (1.22 mL, 8.8 mmol) and trimethylacetyl chloride (0.53 mL, 4.4 mmol) dropwise at 0 °C. The reaction mixture was warmed to room temperature over 16 hours and quenched by the addition of saturated aqueous NaHCO<sub>3</sub> (20 mL). The organic layer was separated and washed with additional saturated aqueous NaHCO<sub>3</sub> (2 x 20 mL), brine (20 mL) and dried over MgSO<sub>4</sub>. The solvent was removed *in vacuo* and the crude oil purified by flash column chromatography (gradient elution: 100% petroleum ether to 30% ethyl acetate in petroleum ether) to afford the product as a colourless oil (0.67 g, 51%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.23; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2932, 2855, 1727, 1602, 1586, 1480, 1461, 1397, 1363, 1282, 1263, 1150, 1083, 1044; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.23 (1 H, t, *J* = 8.1 Hz, H<sub>11</sub>), 6.94 – 6.92 (2 H, m, H<sub>7</sub> and H<sub>12</sub>), 6.80 – 6.77 (1 H, m, H<sub>10</sub>), 4.03 (2 H, s, H<sub>5</sub>), 3.81 (3 H, s, H<sub>9</sub>), 3.63 (2 H, s, H<sub>13</sub>), 1.73 – 1.56 (5 H, m, H<sub>2a</sub>, H<sub>3a</sub> and H<sub>4a</sub>), 1.47 – 1.32 (5 H, m, H<sub>2b</sub>, H<sub>3b</sub> and H<sub>4b</sub>), 1.22 (9 H, s, H<sub>16</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 178.5 (C<sub>14</sub>), 159.8 (C<sub>8</sub>), 143.2 (C<sub>6</sub>), 129.4 (C<sub>11</sub>), 120.7 (C<sub>12</sub>), 114.0 (C<sub>7</sub>), 112.3 (C<sub>10</sub>), 68.1 (C<sub>13</sub>), 55.3 (C<sub>9</sub>), 54.2 (C<sub>1</sub>), 45.9 (C<sub>5</sub>), 39.1 (C<sub>15</sub>), 32.8 (C<sub>2</sub>), 27.4 (C<sub>16</sub>), 26.3 (C<sub>4</sub>), 21.4 (C<sub>3</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 334.2378, C<sub>20</sub>H<sub>32</sub>NO<sub>3</sub> requires 334.2377.

*(1-((4-chlorobenzyl)amino)cyclohexyl)methyl pivalate* **595c**



**Step 1**

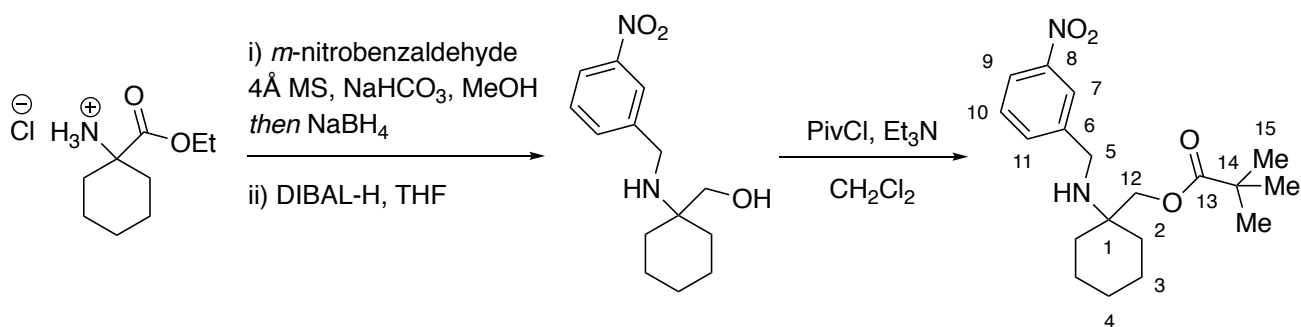
To a solution of ethyl 1-aminocyclohexanecarboxylate hydrochloride **690** (1.03 g, 5.0 mmol), sodium bicarbonate (0.42 g, 5.5 mmol) and powder 4Å MS (1.0 g) in anhydrous methanol (10 mL) as added *p*-chlorobenzaldehyde (0.70 g, 5.0 mmol). The reaction was allowed to stir at room temperature for 16 hours and was subsequently filtered over celite and washed with methanol. The solvent was removed *in vacuo* and dried under vacuum. The resulting residue was dissolved in anhydrous tetrahydrofuran (25 mL) and cooled to 0 °C before lithium aluminium hydride (0.57 g, 15.0 mmol) was added portion-wise. The reaction mixture was warmed to room temperature over 2 hours, cooled to 0 °C and quenched successively with water (0.75 mL), 10% NaOH (1 mL) and water (2 mL). The resulting slurry was stirred with MgSO<sub>4</sub> and filtered. The filter cake was washed with diethyl ether (100 mL) and the combined organics removed *in vacuo* to afford the crude amino alcohol as a white solid (1.23 g, 97%), which was used without further purification. <sup>1</sup>H NMR (400

MHz, CDCl<sub>3</sub>)  $\delta$ : 7.33 – 7.26 (5 H, m), 3.60 (2 H, s), 3.38 (2 H, s), 1.61 – 1.40 (10 H, m).

## Step 2

To a solution of crude amino alcohol (1.01 g, 4.0 mmol) in anhydrous dichloromethane (20 mL) was added triethylamine (1.22 mL, 8.8 mmol) and trimethylacetyl chloride (0.53 mL, 4.4 mmol) dropwise at 0 °C. The reaction mixture was warmed to room temperature over 16 hours and quenched by the addition of saturated aqueous NaHCO<sub>3</sub> (20 mL). The organic layer was separated and washed with additional saturated aqueous NaHCO<sub>3</sub> (2 x 20 mL), brine (20 mL) and dried over MgSO<sub>4</sub>. The solvent was removed *in vacuo* and the crude oil purified by flash column chromatography (gradient elution: 100% petroleum ether to 10% ethyl acetate in petroleum ether) to afford the product as a colourless oil (0.45 g, 33%). *R<sub>f</sub>* (10% ethyl acetate in petroleum ether): 0.44; IR  $\nu_{\text{max}}$ /cm<sup>-1</sup> (film): 2933, 2855, 1727, 1490, 1479, 1461, 1397, 1364, 1282, 1150, 1091, 1034, 1015; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.28 – 7.26 (4 H, m, H<sub>7</sub> and H<sub>8</sub>), 4.02 (2 H, s, H<sub>10</sub>), 3.61 (2 H, s, H<sub>5</sub>), 1.70 – 1.57 (5 H, m, H<sub>2a</sub>, H<sub>3a</sub> and H<sub>4a</sub>), 1.46 – 1.31 (5 H, m, H<sub>2b</sub>, H<sub>3b</sub> and H<sub>4b</sub>), 1.21 (9 H, s, H<sub>13</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 178.5 (C<sub>11</sub>), 140.1 (C<sub>6</sub>), 132.6 (C<sub>9</sub>), 129.7 (C<sub>7</sub>), 128.6 (C<sub>8</sub>), 68.1 (C<sub>10</sub>), 54.3 (C<sub>1</sub>), 45.2 (C<sub>5</sub>), 39.1 (C<sub>12</sub>), 32.8 (C<sub>2</sub>), 27.4 (C<sub>13</sub>), 26.2 (C<sub>4</sub>), 21.4 (C<sub>3</sub>); *m/z* HRMS found [M + H]<sup>+</sup> 338.1884, C<sub>19</sub>H<sub>29</sub>ClNO<sub>2</sub> requires 338.1881.

## (1-((3-nitrobenzyl)amino)cyclohexyl)methyl pivalate **595d**



## Step 1

To a solution of ethyl 1-aminocyclohexanecarboxylate hydrochloride **690** (1.03 g, 5.0 mmol), sodium bicarbonate (0.42 g, 5.5 mmol) and powdered 4Å MS (1.0 g) in anhydrous methanol (10 mL) as added *m*-nitrobenzaldehyde (0.76 g, 5.0 mmol). The reaction was allowed to stir at room temperature for 16 hours and was subsequently cooled to 0 °C. Sodium borohydride (0.28 g, 7.5 mmol) was cautiously added portion-wise and the mixture was allowed to warm to room temperature over 2 hours. The reaction mixture was filtered over celite, washed with methanol and the solvent removed *in vacuo* to afford the amino ester as a yellow oil (1.45 g, 95%), which was used without

further purification.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.23 (1 H, app s), 8.09 (1 H, dd,  $J = 1.6, 8.2$  Hz), 7.68 (1 H, d,  $J = 7.5$  Hz), 7.47 (1 H, t,  $J = 8.0$  Hz), 4.20 (2 H, q,  $J = 7.1$  Hz), 3.70 (2 H, s), 1.95 – 1.89 (2 H, m), 1.75 – 1.37 (8 H, m), 1.30 (3 H, t,  $J = 7.1$  Hz).

## Step 2

To a solution of the crude amino ester (1.38 g, 4.5 mmol) in anhydrous tetrahydrofuran (20 mL) at 0 °C was added DIBAL-H (1 M in tetrahydrofuran, 13.5 mL, 13.5 mmol) dropwise. The resulting solution was allowed to warm to room temperature over 16 hours. The solution was cooled to 0 °C and quenched with a saturated solution of Rochelle's salt (20 mL). The mixture was allowed to stir at room temperature for 3 hours and the organic layer was separated. The aqueous was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers washed with brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. The resulting solid was purified by flash column chromatography (gradient elution: 5% EtAOc in petroleum ether to 50% ethyl acetate in petroleum ether) to afford the amino alcohol as a pale yellow solid (0.58 g, 49%).  $R_f$  (30% ethyl acetate in petroleum ether): 0.16;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.22 (1 H, app s), 8.11 (1 H, dd,  $J = 1.3, 8.2$  Hz), 7.70 (1 H, d,  $J = 7.6$  Hz), 7.50 (1 H, t,  $J = 7.9$  Hz), 3.76 (2 H, s), 3.42 (2 H, s), 1.97 (1 H, br s), 1.63 – 1.41 (10 H, m);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 148.5, 143.1, 134.5, 129.5, 123.0, 22.3, 65.4, 55.7, 44.6, 32.8, 26.1, 21.8;  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  265.1549,  $\text{C}_{14}\text{H}_{21}\text{N}_2\text{O}_3$  requires 265.1547.

## Step 3

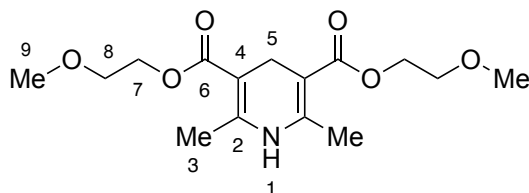
To a solution of crude amino alcohol (0.58 g, 2.2 mmol) in anhydrous dichloromethane (10 mL) was added triethylamine (0.67 mL, 4.8 mmol) and trimethylacetyl chloride (0.30 mL, 2.4 mmol) dropwise at 0 °C. The reaction mixture was warmed to room temperature over 16 hours and quenched by the addition of saturated aqueous  $\text{NaHCO}_3$  (10 mL). The organic layer was separated and washed with additional saturated aqueous  $\text{NaHCO}_3$  (2 x 10 mL), brine (10 mL) and dried over  $\text{MgSO}_4$ . The solvent was removed *in vacuo* and the crude oil purified by flash column chromatography (gradient elution: 100% petroleum ether to 25% ethyl acetate in petroleum ether) to afford the product as a colourless oil (0.47 g, 61%).  $R_f$  (10% ethyl acetate in petroleum ether): 0.29; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2932, 2856, 1725, 1527, 1479, 1461, 1397, 1348, 1282, 1151, 1094, 1034;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.25 (1 H, app s,  $\text{H}_7$ ), 8.09 (1 H, dd,  $J = 1.0, 8.0$  Hz,  $\text{H}_9$ ), 7.70 (1 H, d,  $J = 7.8$  Hz,  $\text{H}_{11}$ ), 7.45 (1 H, t,  $J = 7.8$  Hz,  $\text{H}_{10}$ ), 4.04 (2 H, s,  $\text{H}_5$ ), 3.77 (2 H, s,  $\text{H}_{12}$ ), 1.67 – 1.56 (5 H, m,  $\text{H}_{2a}$ ,  $\text{H}_{3a}$  and  $\text{H}_{4a}$ ), 1.50 – 1.38 (5 H, m,  $\text{H}_{2b}$ ,  $\text{H}_{3b}$  and  $\text{H}_{4b}$ ), 1.22 (9 H, s,  $\text{H}_{15}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 178.5 ( $\text{C}_{13}$ ), 148.5 ( $\text{C}_8$ ), 143.5 ( $\text{C}_6$ ), 134.5 ( $\text{C}_{11}$ ), 129.3 ( $\text{C}_{10}$ ), 123.2 ( $\text{C}_7$ ), 122.1 ( $\text{C}_9$ ), 68.0



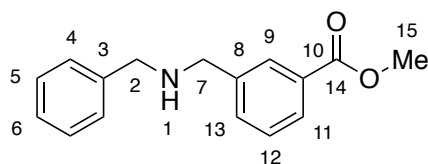
(C<sub>12</sub>), 54.5 (C<sub>1</sub>), 45.2 (C<sub>5</sub>), 39.2 (C<sub>14</sub>), 32.8 (C<sub>2</sub>), 27.4 (C<sub>15</sub>), 26.2 (C<sub>4</sub>), 21.4 (C<sub>3</sub>); m/z HRMS found [M + H]<sup>+</sup> 349.2122, C<sub>19</sub>H<sub>29</sub>N<sub>2</sub>O<sub>4</sub> requires 349.2122.

v) *Synthesis of Hantzsch esters*

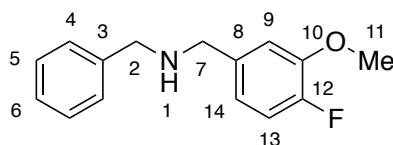
*bis(2-methoxyethyl) 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (MeOEt-HEH) 665*



A 250 mL round bottom flask equipped with magnetic stirrer bar, reflux condenser and N<sub>2</sub> inlet was charged with paraformaldehyde (0.60 g, 20 mmol) and ammonium acetate (3.08 g, 40 mmol). The flask was sealed and evacuated/backfilled (3 cycles). water (40 mL) and methoxyethyl acetoacetate (11.8 mL, 80 mmol) was added and the reaction mixture was sparged with N<sub>2</sub> for 45 minutes. The reaction was heated to reflux for 3 hours and then cooled slowly to facilitate crystallization in the dark. The solid was broken up, filtered and washed with a minimum of ice cold water (50 mL) and ice cold isopropanol (50 mL) so as to remove the bright canary yellow oxidized pyridine by-product. The resulting pale yellow/iridescent dihydropyridine product was obtained as a microcrystalline solid (2.36 g, 38%, >95% purity). The solid was stored in the dark under N<sub>2</sub> at -20 °C for a period of months without deterioration. m.p. 100 – 101 °C. IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (neat): 3342, 3254, 3109, 3030, 2883, 2822, 1693, 1646, 1626, 1504, 1450, 1404, 1376, 1351, 1319, 1300, 1258, 1241, 1218, 1200, 1096, 1050, 1017. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 5.43 (1 H, br s, N-H<sub>1</sub>), 4.23 (4 H, t, *J* = 4.8 Hz, H<sub>7</sub>), 3.61 (4 H, t, *J* = 4.8 Hz, H<sub>8</sub>), 3.37 (6 H, s, H<sub>9</sub>), 3.28 (2 H, s, H<sub>5</sub>), 2.17 (6 H, s, H<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : 168.0 (C<sub>6</sub>), 145.5 (C<sub>2</sub>), 99.3 (C<sub>4</sub>), 70.8 (C<sub>8</sub>), 63.0 (C<sub>7</sub>), 59.1 (C<sub>9</sub>), 24.9 (C<sub>5</sub>), 19.2 (C<sub>3</sub>); m/z HRMS found [M + H]<sup>+</sup> 314.1595, C<sub>15</sub>H<sub>24</sub>NO<sub>6</sub> requires 314.1598.

vi) *Synthesis of Starting Amines for Photocatalytic Reductive Alkylation**methyl 3-((benzylamino)methyl)benzoate 671a*

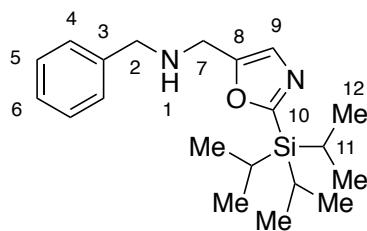
General procedure D was applied to methyl 3-formylbenzoate (0.82 g, 5.0 mmol) and benzylamine (0.55 mL, 5.0 mmol) in dichloromethane (20 mL). The mixture was left to stir at room temperature for 24 hours. The resulting oil was purified using flash column chromatography (gradient elution: 100% petroleum ether to 30% ethyl acetate in petroleum ether) to afford the desired amine as a colourless oil (0.61 g, 48%).  $R_f$  (30% ethyl acetate in petroleum ether): 0.21; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 3027, 2950, 2835, 1717, 1604, 1588, 1494, 1433, 1360, 1281, 1199, 1105, 1083, 1028.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.05 (1 H, s, H<sub>8</sub>), 7.96 (1 H, d,  $J = 7.7$  Hz, H<sub>11</sub>), 7.59 (1 H, d,  $J = 7.6$  Hz, H<sub>13</sub>), 7.43 (1 H, t,  $J = 7.7$  Hz, H<sub>12</sub>), 7.37 (4 H, d,  $J = 4.2$  Hz, H<sub>4</sub> and H<sub>5</sub>), 7.32 – 7.26 (1 H, m, H<sub>6</sub>), 3.94 (3 H, s, H<sub>15</sub>), 3.88 (2 H, s, H<sub>7</sub>), 3.84 (2 H, s, H<sub>4</sub>), 1.76 (br s, N-H<sub>1</sub>);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 167.3 (C<sub>14</sub>), 140.9 (C<sub>8</sub>), 140.2 (C<sub>3</sub>), 132.9 (C<sub>13</sub>), 130.4 (C<sub>10</sub>), 129.4 (C<sub>9</sub>), 128.6 (C<sub>4</sub>), 128.6 (C<sub>12</sub>), 128.4 (C<sub>5</sub>), 128.3 (C<sub>11</sub>), 127.2 (C<sub>6</sub>), 53.3 (C<sub>2</sub>), 52.9 (C<sub>7</sub>), 52.2 (C<sub>15</sub>);  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  256.1330,  $\text{C}_{16}\text{H}_{18}\text{NO}_2$  requires 256.1332.

*N-benzyl-1-(4-fluoro-3-methoxyphenyl)methanamine 671b*

General procedure D was applied to 4-fluoro-3-methoxybenzaldehyde (0.77 g, 5.0 mmol) and benzylamine (0.55 mL, 5.0 mmol) in dichloromethane (20 mL). The resulting oil was purified using flash column chromatography (gradient elution: 30% ethyl acetate in petroleum ether to 50% ethyl acetate in petroleum ether) to afford the desired amine as a colourless oil (0.63 g, 51%).  $R_f$  (50% ethyl acetate in petroleum ether): 0.19; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 3026, 2937, 2832, 1609, 1513, 1452, 1417, 1360, 1278, 1213, 1189, 1151, 1117, 1031.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.37 (4 H, d  $J = 4.4$  Hz, H<sub>4</sub> and H<sub>5</sub>), 7.32 – 7.27 (1 H, m, H<sub>6</sub>), 7.04 (2 H, app dd,  $J = 8.2, 11.2$  Hz, H<sub>9</sub> and H<sub>13</sub>), 6.88 – 6.85 (1 H, m, H, H<sub>14</sub>), 3.92 (3 H, s, H<sub>11</sub>), 3.83 (2 H, s, H<sub>2</sub>), 3.79 (2 H, s, H<sub>7</sub>), 1.70 (br s, N-H<sub>1</sub>);  $^{13}\text{C}$

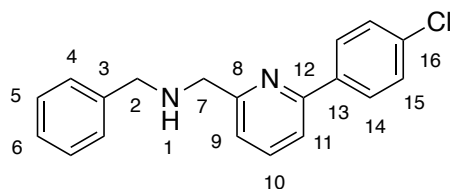
NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 151.6 (d,  $J$  = 246 Hz, C<sub>12</sub>), 147.7 (d,  $J$  = 11 Hz, C<sub>10</sub>), 140.3 (C<sub>3</sub>), 136.8 (d,  $J$  = 3.8 Hz, C<sub>8</sub>), 128.6 (C<sub>4</sub>), 128.3 (C<sub>5</sub>), 127.2 (C<sub>6</sub>), 120.4 (d,  $J$  = 6.7 Hz, C<sub>14</sub>), 115.8 (d,  $J$  = 18 Hz, C<sub>13</sub>), 113.4 (d,  $J$  = 1.9 Hz, C<sub>9</sub>), 56.3 (C<sub>11</sub>), 53.3 (C<sub>2</sub>), 52.9 (C<sub>7</sub>); <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$ : -193.0;  $m/z$  HRMS found  $[M + H]^+$  246.1290, C<sub>15</sub>H<sub>17</sub>FNO requires 246.1289.

*N*-benzyl-1-(2-(triisopropylsilyl)oxazol-5-yl)methanamine **671d**



General procedure D was applied to 2-(triisopropylsilyl)oxazole-5-carbaldehyde (0.39 mL, 1.5 mmol) and benzylamine (0.20 mL, 1.8 mmol) in dichloromethane (10 mL). The resulting oil was purified using flash column chromatography (gradient elution: 100% petroleum ether to 30% ethyl acetate in petroleum ether) to afford the desired amine as a colourless oil that turned pale yellow on standing (0.25 g, 48%).  $R_f$  (30% ethyl acetate in petroleum ether): 0.24; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2943, 2866, 1495, 1462, 1384, 1366, 1117, 1073, 1019. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.35 – 7.30 (5 H, m, H<sub>4</sub>, H<sub>5</sub> and H<sub>6</sub>), 7.28 – 7.25 (1 H, m, H<sub>9</sub>), 3.89 (2 H, d,  $J$  = 0.8 Hz, H<sub>2</sub>), 3.78 (2 H, s, H<sub>7</sub>), 1.68 (br s, N-H<sub>1</sub>), 1.41 (3 H, spt,  $J$  = 7.5 Hz, H<sub>11</sub>), 1.14 (18 H, d,  $J$  = 7.5 Hz, H<sub>12</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 168.4 (C<sub>10</sub>), 152.8 (C<sub>8</sub>), 139.7 (C<sub>3</sub>), 128.6 (C<sub>4</sub>), 128.4 (C<sub>5</sub>), 127.3 (C<sub>6</sub>), 124.2 (C<sub>9</sub>), 52.8 (C<sub>2</sub>), 43.2 (C<sub>7</sub>), 18.5 (C<sub>12</sub>), 11.1 (C<sub>11</sub>);  $m/z$  HRMS found  $[M + H]^+$  345.2360, C<sub>20</sub>H<sub>33</sub>N<sub>2</sub>OSi requires 345.2357.

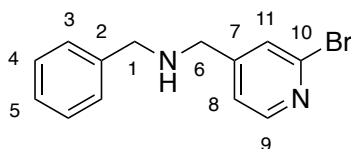
*N*-benzyl-1-(6-(4-chlorophenyl)pyridin-2-yl)methanamine **671e**



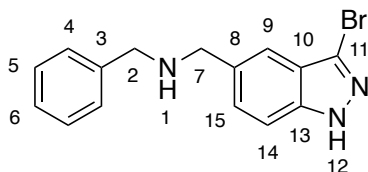
General procedure D was applied to 6-(4-chlorophenyl)-2-pyridinecarboxaldehyde (0.33 g, 1.5 mmol) and benzylamine (0.20 mL, 1.8 mmol) in dichloromethane (10 mL). The resulting oil was purified using flash column chromatography (gradient elution: 30% ethyl acetate in petroleum ether to 60% ethyl acetate in petroleum ether) to afford the desired amine as a colourless oil that turned

yellow on standing (0.39 g, 85%).  $R_f$  (30% ethyl acetate in petroleum ether): 0.15; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 3025, 2833, 1589, 1576, 1564, 1493, 1449, 1391, 1361, 1299, 1180, 1157, 1091, 1027, 1012.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.99 (2 H, dt,  $J = 2.5, 9.1$  Hz,  $\text{H}_{15}$ ), 7.73 (1 H, t,  $J = 7.7$  Hz,  $\text{H}_{10}$ ), 7.60 (1 H, d,  $J = 7.8$  Hz,  $\text{H}_{11}$ ), 7.46 (2 H, dt,  $J = 2.4, 9.1$  Hz,  $\text{H}_{14}$ ), 7.43 – 7.41 (2 H, m,  $\text{H}_4$ ), 7.37 (2 H, t,  $J = 7.1$  Hz,  $\text{H}_5$ ), 7.31 – 7.28 (2 H, m,  $\text{H}_6$  and  $\text{H}_9$ ), 4.02 (2 H, s,  $\text{H}_7$ ), 3.93 (2 H, s,  $\text{H}_2$ ), 2.14 (br s, N- $\text{H}_1$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 159.9 ( $\text{C}_8$ ), 155.7 ( $\text{C}_{12}$ ), 140.4 ( $\text{C}_3$ ), 138.0 ( $\text{C}_{16}$ ), 137.4 ( $\text{C}_{10}$ ), 135.1 ( $\text{C}_{13}$ ), 129.0 ( $\text{C}_{14}$ ), 128.6 ( $\text{C}_{15}$  or  $\text{C}_4$  or  $\text{C}_5$ ), 128.4 ( $\text{C}_{15}$  or  $\text{C}_4$  or  $\text{C}_5$ ), 128.3 ( $\text{C}_{15}$  or  $\text{C}_4$  or  $\text{C}_5$ ), 127.1 ( $\text{C}_6$ ), 121.0 ( $\text{C}_9$ ), 118.6 ( $\text{C}_{11}$ ), 54.6 ( $\text{C}_7$ ), 53.7 ( $\text{C}_2$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  309.1148  $\{\text{}^{35}\text{Cl}\}$ ,  $\text{C}_{19}\text{H}_{18}\text{ClN}_2$  requires 309.1153  $\{\text{}^{35}\text{Cl}\}$ .

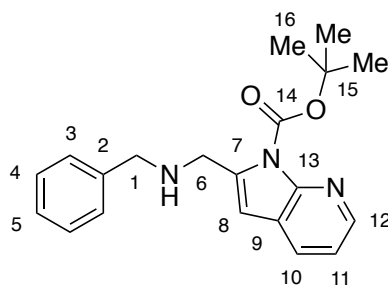
*N*-benzyl-1-(2-bromopyridin-4-yl)methanamine **671f**



General procedure D was applied to 2-bromopyridine-4-carboxaldehyde (0.50 g, 2.7 mmol) and benzylamine (0.35 mL, 3.2 mmol) in dichloromethane (10 mL). The resulting oil was purified using flash column chromatography (gradient elution: 30% ethyl acetate in petroleum ether to 50% ethyl acetate in petroleum ether) to afford the desired amine as a colourless oil that turned pale brown on standing (0.68 g, 91%).  $R_f$  (50% ethyl acetate in petroleum ether): 0.40; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 3308, 3027, 2829, 1587, 1542, 1494, 1453, 1378, 1200, 1114, 1073, 1027.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.29 (1 H, d,  $J = 4.9$  Hz,  $\text{H}_9$ ), 7.53 (1 H, s,  $\text{H}_{11}$ ), 7.38 – 7.25 (6 H, m,  $\text{H}_3$ ,  $\text{H}_4$ ,  $\text{H}_5$  and  $\text{H}_8$ ), 3.81 (2 H, s,  $\text{H}_1$  or  $\text{H}_6$ ), 3.81 (2 H, s,  $\text{H}_1$  or  $\text{H}_6$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 153.0 ( $\text{C}_{10}$ ), 150.1 ( $\text{C}_9$ ), 142.7 ( $\text{C}_7$ ), 139.7 ( $\text{C}_2$ ), 128.7 ( $\text{C}_3$ ), 128.2 ( $\text{C}_4$ ), 127.4 ( $\text{C}_{11}$ ), 127.3 ( $\text{C}_5$ ), 122.3 ( $\text{C}_8$ ), 53.4 ( $\text{C}_1$ ), 51.4 ( $\text{C}_6$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  277.0339  $\{\text{}^{79}\text{Br}\}$ ,  $\text{C}_{13}\text{H}_{14}\text{BrN}_2$  requires 277.0335  $\{\text{}^{79}\text{Br}\}$ .

*N*-benzyl-1-(3-bromo-1*H*-indazol-5-yl)methanamine **671g**

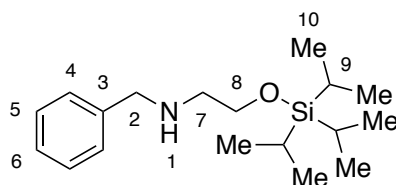
General procedure D was applied to 3-bromo-1*H*-indazole-5-carboxaldehyde (0.25 g, 1.1 mmol) and benzylamine (0.15 mL, 1.3 mmol) in dichloromethane/acetonitrile (15 mL, 2:1). The resulting oil was purified using flash column chromatography (gradient elution: 50% ethyl acetate in petroleum ether to 70% ethyl acetate in petroleum ether) to afford the desired amine as a white gum (0.31 g, 89%).  $R_f$  (70% ethyl acetate in petroleum ether): 0.15; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 3133, 3045, 2909, 2850, 1630, 1584, 1494, 1452, 1363, 1336, 1299, 1255, 1241, 1173, 1105, 1078, 1017.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 10.78 (1 H, br s,  $\text{H}_{12}$ ), 7.57 (1 H, br s,  $\text{H}_{15}$ ), 7.46 (1 H, dd,  $J = 1.2, 8.8$  Hz,  $\text{H}_{14}$ ), 7.41 (1 H, d,  $J = 8.5$  Hz,  $\text{H}_9$ ), 7.38 – 7.33 (4 H, m,  $\text{H}_4$  and  $\text{H}_5$ ), 7.29 – 7.26 (1 H, m,  $\text{H}_6$ ), 3.94 (2 H, s,  $\text{H}_7$ ), 3.86 (2 H, s,  $\text{H}_2$ ), 1.83 (br s, N- $\text{H}_1$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 140.8 ( $\text{C}_{13}$ ), 140.0 ( $\text{C}_3$ ), 134.1 ( $\text{C}_8$ ), 129.3 ( $\text{C}_9$ ), 128.6 ( $\text{C}_4$ ), 128.4 ( $\text{C}_5$ ), 127.3 ( $\text{C}_6$ ), 123.3 ( $\text{C}_{11}$ ), 122.9 ( $\text{C}_{10}$ ), 119.2 ( $\text{C}_{15}$ ), 110.4 ( $\text{C}_{14}$ ), 53.3 ( $\text{C}_2$ ), 53.1 ( $\text{C}_7$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  316.0448  $\{^{79}\text{Br}\}$ ,  $\text{C}_{15}\text{H}_{15}\text{BrN}_3$  requires 316.0444  $\{^{79}\text{Br}\}$ .

*1*-Boc-2-((benzylamino)methyl)-7-azaindole **671h**

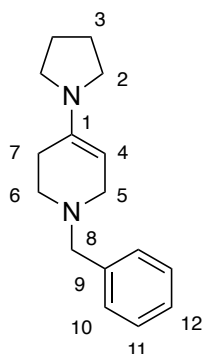
General procedure D was applied to 1-Boc-7-azaindole-3-carboxaldehyde (0.49 g, 2.0 mmol) and benzylamine (0.33 mL, 3.0 mmol) in dichloromethane (10 mL). The resulting oil was purified using flash column chromatography (gradient elution: 20% ethyl acetate in petroleum ether to 70% ethyl acetate in petroleum ether) to afford the desired amine as a colourless oil that turned solid on standing (0.54 g, 80%).  $R_f$  (50% ethyl acetate in petroleum ether): 0.18; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 3281, 3021, 2986, 2909, 1734, 1716, 1607, 1592, 1560, 1493, 1479, 1451, 1407, 1388, 1360, 1315, 1266, 1240, 1150, 1113, 1091, 1054, 1044, 1018.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.53 (1 H, dd,  $J = 1.4, 4.8$

Hz, H<sub>12</sub>), 7.97 (1 H, dd,  $J = 1.5, 7.8$  Hz, H<sub>10</sub>), 7.58 (1 H, s, H<sub>8</sub>), 7.37 (4 H, d,  $J = 4.4$  Hz, H<sub>3</sub> and H<sub>4</sub>), 7.32 – 7.27 (1 H, m, H<sub>5</sub>), 7.20 (1 H, dd,  $J = 4.8, 7.7$  Hz, H<sub>11</sub>), 3.94 (2 H, s, H<sub>6</sub>), 3.89 (2 H, s, H<sub>1</sub>), 1.69 (9 H, s, H<sub>16</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 148.9 (C<sub>13</sub>), 148.0 (C<sub>14</sub>), 145.4 (C<sub>12</sub>), 140.2 (C<sub>2</sub>), 128.6 (C<sub>3</sub>), 128.3 (C<sub>4</sub>), 128.1 (C<sub>10</sub>), 127.2 (C<sub>5</sub>), 124.0 (C<sub>8</sub>), 122.9 (C<sub>7</sub>), 118.4 (C<sub>11</sub>), 117.1 (C<sub>9</sub>), 84.0 (C<sub>15</sub>), 53.7 (C<sub>1</sub>), 44.2 (C<sub>6</sub>), 28.3 (C<sub>16</sub>);  $m/z$  HRMS found  $[M + H]^+$  338.1867, C<sub>20</sub>H<sub>24</sub>N<sub>3</sub>O<sub>2</sub> requires 338.1863.

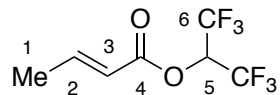
*N*-benzyl-2-((triisopropylsilyl)oxy)ethan-1-amine **671k**



Triisopropylsilyl chloride (1.01 mL, 4.75 mmol) was added dropwise to a solution of *N*-benzylethanolamine (0.71 mL, 5.0 mmol) and triethylamine (1.04 mL, 7.5 mmol) in anhydrous dichloromethane (10 mL) at 0 °C. The resulting solution was allowed to warm to room temperature over 16 hours and was quenched with water (20 mL). The organics were separated and washed with additional water (2 x 20 mL) and brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and removed *in vacuo*. The crude oil was purified by flash column chromatography (gradient elution: 100% petroleum ether to 30% ethyl acetate in petroleum ether) to provide the desired amine as colourless oil (0.63 g, 41%).  $R_f$  (20% ethyl acetate in petroleum ether): 0.19; IR  $\nu_{\max}/\text{cm}^{-1}$  (film): 2942, 2865, 1494, 1454, 1382, 1365, 1248, 1102, 1067. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.37 – 7.32 (4 H, m, H<sub>4</sub> and H<sub>5</sub>), 7.30 – 7.24 (1 H, m, H<sub>6</sub>), 3.87 – 3.85 (4 H, m, H<sub>2</sub> and H<sub>8</sub>), 2.79 (2 H, t,  $J = 5.4$  Hz, H<sub>7</sub>), 1.90 (br s, N-H<sub>1</sub>), 1.17 – 1.06 (21 H, m, H<sub>9</sub> and H<sub>10</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : 140.7 (C<sub>3</sub>), 128.5 (C<sub>4</sub>), 128.1 (C<sub>5</sub>), 126.9 (C<sub>6</sub>), 62.7 (C<sub>8</sub>), 53.9 (C<sub>2</sub>), 51.5 (C<sub>7</sub>), 18.1 (C<sub>10</sub>), 12.1 (C<sub>9</sub>);  $m/z$  HRMS found  $[M + H]^+$  308.2402, C<sub>18</sub>H<sub>34</sub>NOSi requires 308.2404.

vii) *Synthesis of Enamines for Photocatalytic Reductive Alkylation**1-benzyl-4-(pyrrolidin-1-yl)-1,2,3,6-tetrahydropyridine 686d*

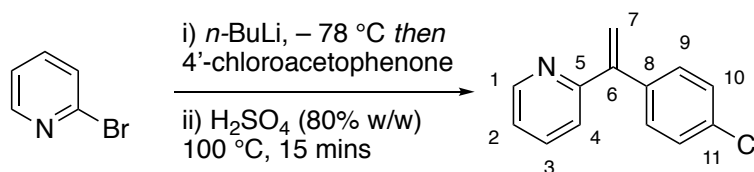
1-benzyl-4-piperidone (11.1 mL, 60 mmol) and pyrrolidine (4.1 mL, 50 mmol) were suspended in anhydrous toluene (30 mL) with toluene-4-sulfonic acid (50 mg). The mixture was refluxed and the water separated using a Dean-Stark trap for 16 hours. After such time, the mixture was cooled and the solvent removed *in vacuo*. The resulting oil was purified by fractional distillation (147 °C, 0.12 mbar) to afford the product as a pale yellow oil (7.0 g, >90% purity by  $^1\text{H}$  NMR, 58%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2098, 2797, 1718, 1648, 1494, 1453, 1389, 1364, 1352, 1338, 1313, 1174, 1125;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.40 (2 H, d,  $J = 7.5$  Hz,  $\text{H}_{10}$ ), 7.33 (2 H, t,  $J = 7.1$  Hz,  $\text{H}_{11}$ ), 7.26 (1 H, m,  $\text{H}_{12}$ ), 4.21 (1 H, t,  $J = 3.5$  Hz,  $\text{H}_4$ ), 3.60 (2 H, s,  $\text{H}_8$ ), 2.10 (2 H, br m,  $\text{H}_5$ ), 3.05 (4 H, t,  $J = 6.5$  Hz,  $\text{H}_2$ ), 2.61 (2 H, t,  $J = 5.7$  Hz,  $\text{H}_6$ ), 2.35 (2 H, t,  $J = 5.9$  Hz,  $\text{H}_7$ ), 1.87 – 1.83 (4 H, m,  $\text{H}_3$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 141.8, 139.0, 129.3, 128.2, 127.0, 90.5, 62.9, 53.2, 50.3, 47.3, 28.5, 24.8; GC-MS: 244 ( $\text{M}+\text{H}^+$ ), 173 (65), 153 (25), 91 (100). Data consistent with literature<sup>644</sup>.

viii) *Synthesis of Alkenes for Photocatalytic Reductive Alkylation**1,1,1,3,3,3-hexafluoropropan-2-yl crotonate 666k*

To a suspension of crotonic acid (1.79 g, 20.8 mmol), 4-(dimethylamino)pyridine (0.61 g, 5 mmol) and *N,N'*-dicyclohexylcarbodiimide (5.16 g, 25 mmol) in anhydrous dichloromethane (50 mL) was added 1,1,1,3,3,3-hexafluoroisopropanol (2.63 mL, 25 mmol) dropwise at 0 °C under  $\text{N}_2$ . The reaction mixture was allowed to warm to room temperature over 16 hours. The solids were removed by vacuum filtration and washed with additional dichloromethane (10 mL). The organics were collected and washed with saturated aqueous  $\text{NH}_4\text{Cl}$  (50 mL) and brine (50 mL) and the solvent

removed *in vacuo*. Purification by kugelrohr (85 °C, 185 mbar) gave the desired amine as a colourless mobile liquid (2.25 g, 46%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 1754, 1657, 1446, 1386, 1356, 1285, 1225, 1194, 1145;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.26 (1 H, dq,  $J = 7.1, 15.6$  Hz,  $\text{H}_5$ ), 5.99 (1 H, dq,  $J = 1.6, 16.6$  Hz,  $\text{H}_3$ ), 5.84 (1 H, qt,  $J = 6.2$  Hz,  $\text{H}_2$ ), 2.00 (3 H, dd,  $J = 1.8, 7.0$  Hz,  $\text{H}_1$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 162.8 ( $\text{C}_4$ ), 150.5 ( $\text{C}_2$ ), 120.6 (dq,  $J = 2.8, 282.1$  Hz,  $\text{C}_6$ ), 119.7 ( $\text{C}_3$ ), 66.5 (qt,  $J = 34.3$  Hz,  $\text{C}_5$ ), 18.5 ( $\text{C}_1$ );  $^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$ : -74.4;  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  237.0343,  $\text{C}_7\text{H}_6\text{F}_2\text{O}_2$  requires 237.0345.

### 2-(1-(4-chlorophenyl)vinyl)pyridine **666ak**



#### Step 1

To a solution of 2-bromopyridine (2.38 mL, 25 mmol) in anhydrous diethyl ether (100 mL) at  $-78\text{ }^\circ\text{C}$  under  $\text{N}_2$  was added  $n\text{-BuLi}$  (2.5 M in hexane, 10 mL, 25 mmol) slowly dropwise. The solution was stirred at  $-78\text{ }^\circ\text{C}$  for 45 minutes after which time a solution of 4-chloroacetophenone (3.4 mL, 26.3 mmol) in anhydrous diethyl ether (20 mL) was added slowly dropwise over 20 minutes. The mixture was allowed to stir at  $-78\text{ }^\circ\text{C}$  for 16 hours and was subsequently warmed to  $-20\text{ }^\circ\text{C}$ . The reaction mixture was quenched by the addition of sat. aqueous  $\text{NH}_4\text{Cl}$  (100 mL) and the reaction warmed to room temperature. The layers were separated and the aqueous extracted with additional diethyl ether (2 x 50 mL). The organics were combined and acidified with 3 M  $\text{HCl}$  (100 mL). The aqueous was washed with diethyl ether (2 x 100 mL) and basified with 10% aqueous  $\text{NaOH}$  until  $\text{pH} = 10$ . The aqueous was then extracted with diethyl ether (3 x 100 mL), washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and the solvent removed *in vacuo* to afford 1-(4-chlorophenyl)-1-(pyridin-2-yl)ethan-1-ol as a viscous oil that was used without further purification (3.92 g, 67%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.55 (1 H, d,  $J = 4.8$  Hz), 7.68 (1 H, td,  $J = 1.7, 7.8$  Hz), 7.44 (2 H, d,  $J = 8.5$  Hz), 7.29 (2 H, d,  $J = 8.5$  Hz), 7.22 (1 H, ddd,  $J = 1.0, 4.9, 5.7$  Hz), 5.85 (1 H, s), 1.93 (3 H, s).

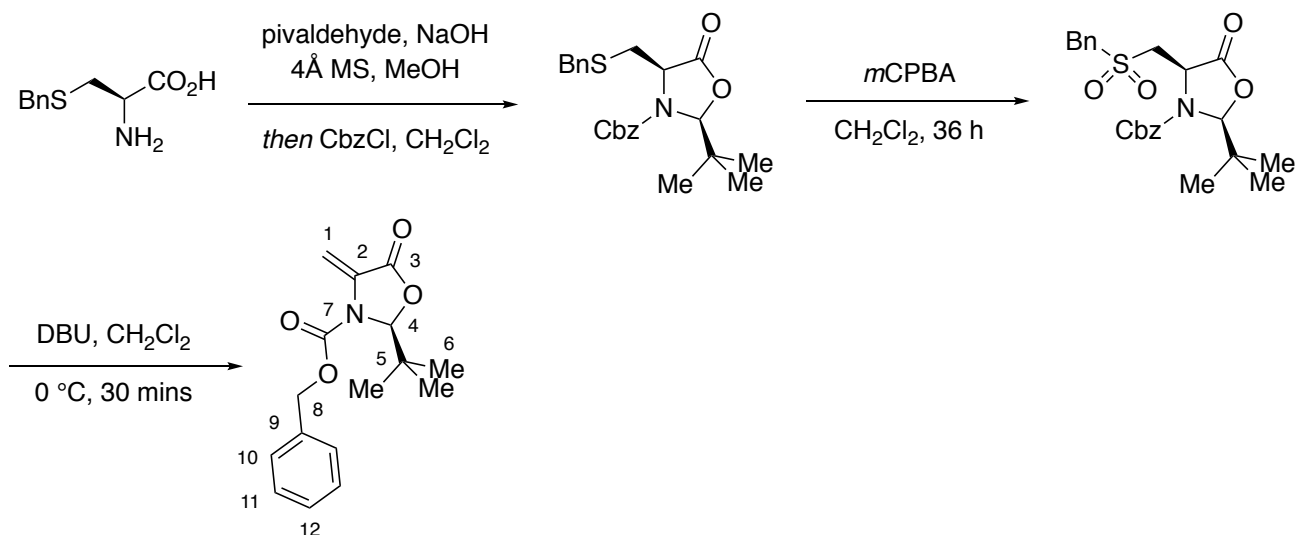
#### Step 2

1-(4-chlorophenyl)-1-(pyridin-2-yl)ethan-1-ol (3.9 g, 16.8 mmol) was added to 80% w/v sulfuric acid (13 mL) and heated to  $100\text{ }^\circ\text{C}$  for 15 minutes. The reaction was subsequently cooled to room temperature and poured onto 100 mL crushed ice. The solution was neutralized with 10% aqueous  $\text{NaOH}$  and extracted with ethyl acetate (3 x 100 mL). The organics were washed with brine, dried



over  $\text{Na}_2\text{SO}_4$  and the solvent removed *in vacuo*. The crude oil was purified by flash column chromatography (gradient elution: 100% petroleum ether to 30% ethyl acetate in petroleum ether) to afford the product as a pale yellow oil that turned dark red upon standing (2.71 g, 75%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3054, 1664, 1583, 1563, 1488, 1466, 1430, 1393, 1332, 1281, 1243, 1153, 1090, 1047, 1013;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.65 (1 H, d,  $J = 4.5$  Hz,  $\text{H}_1$ ), 7.67 (1 H, td,  $J = 1.8, 7.8$  Hz,  $\text{H}_3$ ), 7.27 – 7.28 (5 H, m,  $\text{H}_4, \text{H}_9$  and  $\text{H}_{10}$ ), 7.24 (1 H, ddd,  $J = 0.9, 4.8, 7.5$  Hz,  $\text{H}_2$ ), 5.98 (1 H, d,  $J = 1.0$  Hz,  $\text{H}_{7a}$ ), 5.62 (1 H, d,  $J = 1.0$  Hz,  $\text{H}_{7b}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 158.3 ( $\text{C}_5$ ), 149.5 ( $\text{C}_1$ ), 148.3 ( $\text{C}_8$ ), 138.9 ( $\text{C}_6$ ), 136.5 ( $\text{C}_3$ ), 133.8 ( $\text{C}_{11}$ ), 129.8 ( $\text{C}_9$  or  $\text{C}_{10}$ ), 128.6 ( $\text{C}_9$  or  $\text{C}_{10}$ ), 122.8 ( $\text{C}_4$ ), 122.7 ( $\text{C}_2$ ), 118.1 ( $\text{C}_7$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  216.0574  $\{^{35}\text{Cl}\}$ ,  $\text{C}_{13}\text{H}_{11}\text{ClN}$  requires 216.0575  $\{^{35}\text{Cl}\}$ . Data consistent with literature<sup>645</sup>.

*(S)*-2-(*tert*-butyl)-3-Cbz-4-methyleneoxazolidin-5-one **668**



**Step 1**

Powdered sodium hydroxide (0.9 g, 22.3 mmol) was added to a suspension of (*S*)-benzyl-L-cysteine (5.0 g, 23.5 mmol) in anhydrous methanol (250 mL) under  $\text{N}_2$ . The suspension was stirred at room temperature until the mixture became homogenous (10 mins) and pivaldehyde (3.1 mL, 28.2 mmol) and 4Å MS (25 g) were added. The mixture was stirred overnight and subsequently filtered rapidly over celite. The solvent was removed *in vacuo* and the resulting oil was dried under hi-vac for a minimum of 4 hours, over which time the oil solidified to a white powder. The imine was subsequently dissolved in anhydrous dichloromethane (250 mL), cooled to 0 °C and CbzCl (5.1 mL, 35.5 mmol) was added slowly dropwise. The mixture was stirred at 0 °C for 18 hours and warmed to room temperature over 6 hours. The mixture was washed with 1 M NaOH (25 mL), dried over  $\text{Na}_2\text{SO}_4$  and the solvent removed *in vacuo*. The crude oil was purified by flash column

chromatography (gradient elution: 5% ethyl acetate in petroleum ether to 15% ethyl acetate in petroleum ether) to afford the product as a colourless viscous oil (2.8 g, 29%, d.r. > 12:1).  $R_f$  (20% ethyl acetate in petroleum ether): 0.5;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.40 (5 H, app br s), 7.32 – 7.25 (5 H, m), 5.56 (1 H, s), 5.25 (1 H, d,  $J = 12.3$  Hz), 5.20 (1 H, d,  $J = 12.0$  Hz), 4.56 (1 H, t,  $J = 6.8$  Hz), 3.80 (2 H, qt,  $J = 13.4$  Hz), 2.95 (1 H, dd,  $J = 8.0, 14.1$  Hz), 2.81 (1 H, dd,  $J = 6.2, 13.9$  Hz), 0.94 (9 H, s);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 171.3, 156.0, 137.8, 135.2, 129.1, 128.8, 128.6, 128.6, 127.2, 96.4, 68.6, 57.7, 37.0, 36.6, 33.4, 24.9. Data consistent with literature<sup>606</sup>.

## Step 2

To a solution of benzyl (2*S*,4*R*)-4-((benzylthio)methyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate (2.4 g, 6 mmol) from Step 1 in dichloromethane (200 mL) was added freshly purified *m*CPBA (2.5 g, 15 mmol). The mixture was allowed to stir at room temperature for 36 hours. The solution was washed with 1 M NaOH (3 x 100 mL), the organic layer dried over  $\text{Na}_2\text{SO}_4$  and the solvent removed *in vacuo* to afford the product as a white foam (2.3 g, 86%) which was used without further purification.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.42 – 7.34 (10 H, m), 5.62 (1 H, s), 5.28 (1 H, d,  $J = 11.8$  Hz), 5.21 (1 H, d,  $J = 11.8$  Hz), 5.08 (1 H, dd,  $J = 4.0, 8.1$  Hz), 4.66 (1 H, d,  $J = 13.8$  Hz), 4.42 (1 H, d,  $J = 14.1$  Hz), 3.44 (1 H, dd,  $J = 8.1, 15.1$  Hz), 3.15 (1 H, dd,  $J = 3.8, 15.1$  Hz), 0.89 (9 H, s);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 170.8, 155.5, 135.0, 131.0, 129.3, 129.2, 129.0, 128.9, 128.9, 128.0, 97.0, 69.1, 60.5, 53.8, 52.8, 37.2, 24.7. Data consistent with literature<sup>606</sup>.

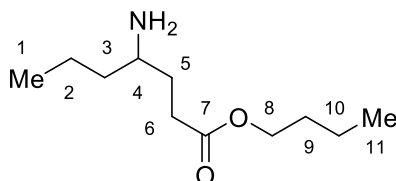
## Step 3

To a solution of benzyl (2*S*,4*R*)-4-((benzylsulfonyl)methyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate (1.8 g, 4.0 mmol) from Step 2 in anhydrous dichloromethane (50 mL) was added dropwise DBU (0.65 mL, 4.4 mmol) at 0 °C under  $\text{N}_2$ . The reaction stirred at 0 °C and was monitored by TLC until complete consumption of the starting material (15 minutes). The reaction mixture was quenched by the addition of sat. aqueous  $\text{NH}_4\text{Cl}$  (25 mL) at 0 °C and the mixture allowed to warm to room temperature. The organic layer was separated and washed with sat. aqueous  $\text{NH}_4\text{Cl}$  (3 x 50 mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$  and the solvent removed *in vacuo*. The resulting oil was purified by flash column chromatography (gradient elution: 100% petroleum ether to 10% ethyl acetate in petroleum ether) to afford the product as a colourless crystalline solid (1.06 g, 92%).  $R_f$  (15% ethyl acetate in petroleum ether): 0.53; m.p. 57 – 61 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.38 (5 H, app br s,  $\text{H}_{10}$ ,  $\text{H}_{11}$  and  $\text{H}_{12}$ ), 5.72 (1 H, s,  $\text{H}_4$ ), 5.68 (2 H, br s,  $\text{H}_1$ ), 5.26 (2 H, d,  $J = 1.2$  Hz,  $\text{H}_8$ ), 0.93 (9 H, s,  $\text{H}_6$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 164.7, 134.8,

130.3, 129.0, 128.9, 128.8, 104.5, 94.1, 68.9, 38.8, 24.4;  $m/z$  HRMS found  $[M + H]^+$  290.1384,  $C_{25}H_{36}NO_2$  requires 290.1387. HPLC (IC, 2%  $i$ PrOH in  $n$ -hexane, 1 mL/min) indicated 95% e.e.:  $t_R$  ( $S$ ) = 14.61 minutes,  $t_R$  ( $R$ ) = 19.02 minutes. Data consistent with literature<sup>606</sup>.

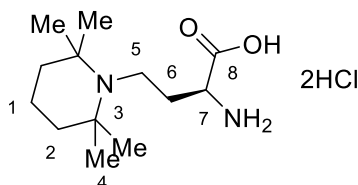
ix) Miscellaneous compounds

butyl 4-aminoheptanoate **683**



To a solution of butyl 4-(dibenzylamino)heptanoate (114 mg, 0.3 mmol) in absolute ethanol (10 mL) was added Pearlman's catalyst (98 mg, 10 mol%) followed by acetic acid (3 drops). The flask was sealed with a septum and a hydrogen balloon was placed on top. The system was evacuated/backfilled (3 cycles) and stirred vigorously at room temperature for 6 hours. The reaction mixture was filtered through celite<sup>®</sup> and the solvent removed *in vacuo* to afford the product as a colourless oil (58 mg, 95%). *Product rapidly cyclizes at room temperature.*  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$ : 4.05 (2 H, t,  $J$  = 6.7 Hz,  $H_8$ ), 2.73 – 2.67 (1 H, br m,  $H_4$ ), 2.42 – 2.28 (2 H, m,  $H_6$ ), 1.80 – 1.72 (1 H, m,  $H_{5a}$ ), 1.62 – 1.48 (3 H, m,  $H_{5b}$  and  $H_9$ ), 1.44 – 1.16 (8 H, m,  $H_2$ ,  $H_3$ ,  $H_9$  and  $H_{10}$ ), 0.93 – 0.88 (6 H, m,  $H_1$  and  $H_{11}$ );  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$ : 174.1 ( $C_7$ ), 64.3 ( $C_8$ ), 50.6 ( $C_4$ ), 40.5 ( $C_3$ ), 33.1 ( $C_5$ ), 31.3 ( $C_6$ ), 30.8 ( $C_9$ ), 19.3 ( $C_2$  or  $C_{10}$ ), 19.3 ( $C_2$  or  $C_{10}$ ), 14.2 ( $C_1$  or  $C_{11}$ ), 13.8 ( $C_1$  or  $C_{11}$ );  $m/z$  HRMS found  $[M + H]^+$  202.1801,  $C_{11}H_{24}NO_2$  requires 202.1802.

(*S*)-2-amino-4-(2,2,6,6-tetramethylpiperidin-1-yl)butanoic acid dihydrochloride **691**



A solution of (2*S*,4*S*)-2-(*tert*-butyl)-3-Cbz-4-(2-(2,2,6,6-tetramethylpiperidin-1-yl)ethyl)oxazolidin-5-one (57 mg, 0.13 mmol) in concentrated HCl (1 mL) was heated to 80 °C for 30 minutes. After which time the solvent was removed *in vacuo* to afford the product as a white powder (38 mg, 95%). m.p. 205 – 210 °C (decomp); IR  $\nu_{max}/cm^{-1}$  (film): 3342 (br), 2951 (br), 2629 (br), 1732, 1598, 1463,

1433, 1413, 1394, 1221, 1169, 1115, 1088.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$ : 4.21 (1 H, s,  $\text{H}_7$ ), 3.57 (1 H, app t,  $J = 12.2$  Hz,  $\text{H}_{5a}$ ), 3.47 (1 H, app t,  $J = 11.8$  Hz,  $\text{H}_{5b}$ ), 2.51 (1 H, br m,  $\text{H}_{6a}$ ), 2.41 (1 H, br m,  $\text{H}_{6b}$ ), 2.04 – 1.93 (3 H, m,  $\text{H}_{1a}$  and  $\text{H}_{2a}$ ), 1.81 (2 H, d,  $J = 13.3$  Hz,  $\text{H}_{2b}$ ), 1.68 (1 H, d,  $J = 13.3$  Hz,  $\text{H}_{1b}$ ), 1.54 (2 H, s,  $\text{H}_{4a}$ ), 1.53 (2 H, s,  $\text{H}_{4b}$ ), 1.47 (2 H, s,  $\text{H}_{4c}$ ), 1.46 (2 H, s,  $\text{H}_{4d}$ ), 1.22 (4 H, s,  $\text{H}_{4e}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$ : 170.5 ( $\text{C}_8$ ), 69.5 ( $\text{C}_{3a}$ ), 68.2 ( $\text{C}_{3b}$ ), 68.1 ( $\text{C}_{3c}$ ), 51.4 ( $\text{C}_7$ ), 44.9 ( $\text{C}_5$ ), 38.0 ( $\text{C}_{2a}$ ), 38.0 ( $\text{C}_{2b}$ ), 31.8 ( $\text{C}_6$ ), 31.1 ( $\text{C}_{4a}$ ), 29.4 ( $\text{C}_{4b}$ ), 29.3 ( $\text{C}_{4c}$ ), 21.1 ( $\text{C}_{4d}$ ), 16.6 ( $\text{C}_1$ );  $m/z$  HRMS found  $[\text{M} + \text{H}]^+$  243.2040,  $\text{C}_{13}\text{H}_{27}\text{N}_2\text{O}_2$  requires 243.2067.  $[\alpha]_{\text{D}}^{24} = +3.6$  ( $c = 0.5$ , methanol).

## Appendix II: Supplementary Data

### i) Optimization studies for Pd-catalyzed methylene C–H bond carbonylation

Entry	Ligand (mol %)	Yield (%) <sup>a</sup>	Entry	Ligand (mol %)	Yield (%) <sup>a</sup>
1	Xantphos (10)	43	4 <sup>‡</sup>	2,2'-diquinolyl (20)	42
2	Xantphos (20)	48	5 <sup>‡</sup>	2,2'-diquinolyl (30)	46
3	Xantphos (40)	30	6 <sup>‡</sup>	2,2'-diquinolyl (100)	46

**Table 24** | Evaluation of ligands for Pd-catalyzed amine carbonylation. <sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane. <sup>‡</sup>Reaction conducted by Dr J. Cabrera-Pardo

Entry	Solvent (temp °C)	Yield (%) <sup>a</sup>	Entry	Solvent (temp °C)	Yield (%) <sup>a</sup>
1	MeCN (85)	11	5	mesitylene (150)	22
2	1,2-DCE (85)	41	6	<i>t</i> -amyl alcohol (85)	trace
3	DMSO (135)	23	7	1,1,2,2-TCE (135)	trace
4	<i>o</i> -xylene (135)	44			

**Table 25** | Evaluation of solvents for Pd-catalyzed amine carbonylation. <sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane

Entry	Ligand	Oxidant (mol %)	Yield (%) <sup>a</sup>
1 <sup>‡</sup>	2,2'-diquinoloyl	AgOAc (300)	8
2 <sup>‡</sup>	2,2'-diquinoloyl	AgSbF <sub>6</sub> (100 + 300)	trace
3 <sup>‡</sup>	2,2'-diquinoloyl	Cu(OAc) <sub>2</sub> (10) <sup>b</sup>	30
4	Xantphos	AgOTf (300)	trace
5	Xantphos	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> (150)	trace

**Table 26** | Evaluation of oxidants for Pd-catalyzed amine carbonylation. <sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane. <sup>b</sup>Reaction conducted using 6.25% CO in air. <sup>‡</sup>Reaction conducted by Dr J. Cabrera-Pardo

CC(C)N(C1CCCCC1)Cc2ccccc2

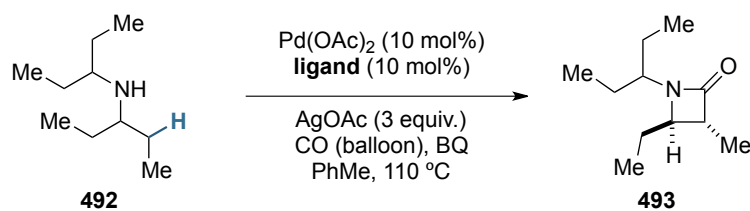
 $\text{Pd(OAc)}_2$  (10 mol%)  
**ligand** (10 mol%)  
  
AgOBz (3 equiv.)  
CO (balloon), BQ  
PhMe, 110 °C

CC1(C)CC(=O)N(C2CCCCC2)C1

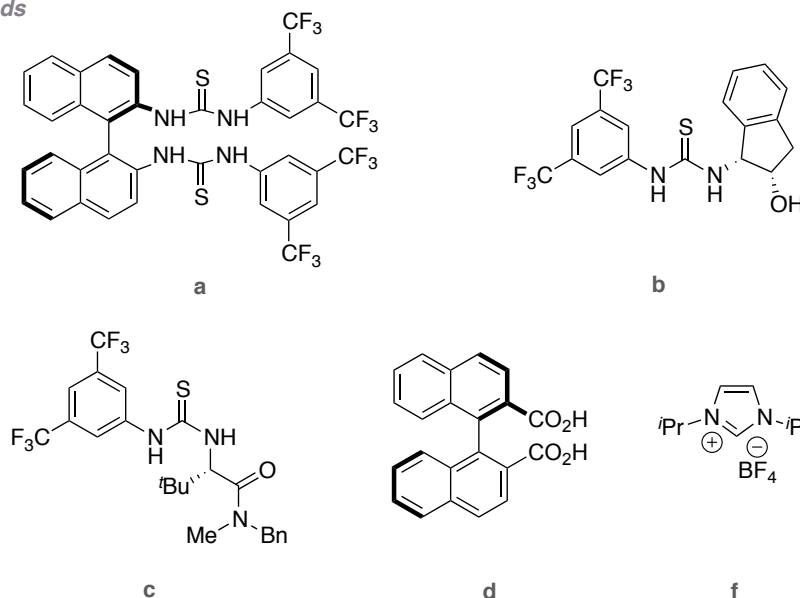
**477**
**479**

Entry	AcOH (mol %)	Yield (%) <sup>a</sup>
1	100	58
2	200	33

**Table 27** | Evaluation of acid additives for Pd-catalyzed amine carbonylation. <sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane

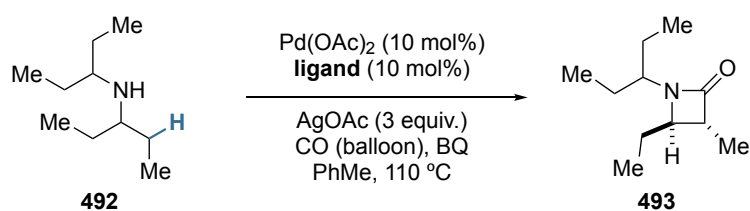


## ligands



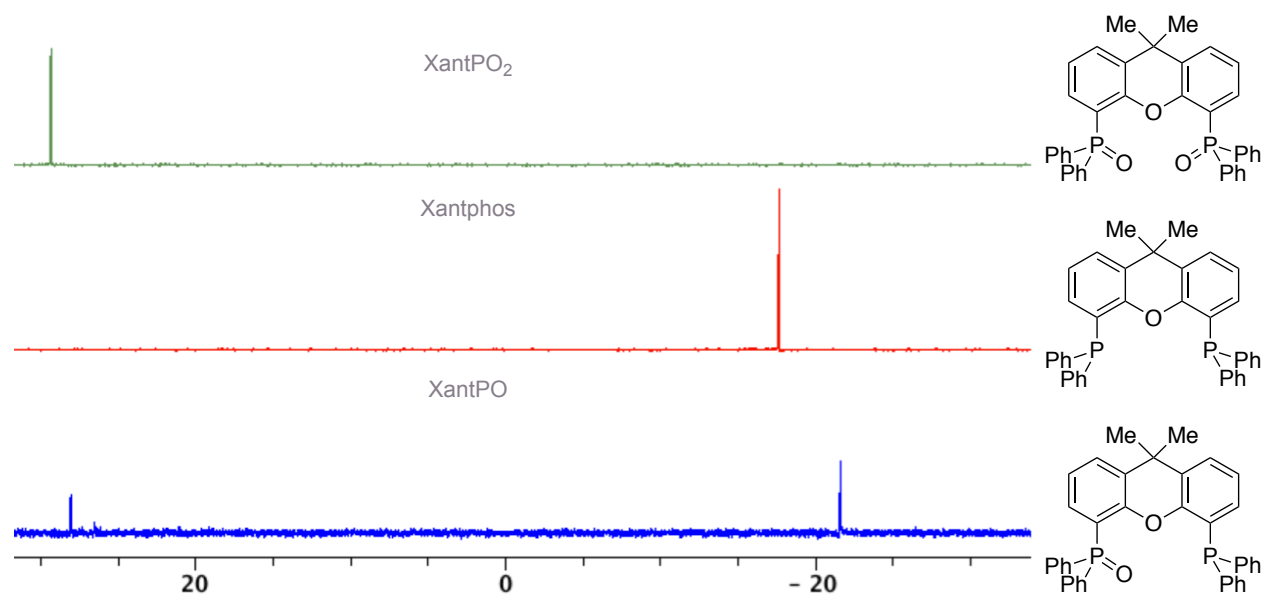
Entry	Ligand	Yield (%) <sup>a</sup>	Entry	Ligand	Yield (%) <sup>a</sup>
1 <sup>‡</sup>	<b>a</b>	6	4 <sup>‡</sup>	<b>d</b>	35
2 <sup>‡</sup>	<b>b</b>	11	5 <sup>‡</sup>	( <i>R</i> )-TRIP	23
3 <sup>‡</sup>	<b>c</b>	2	6 <sup>‡</sup>	<b>f</b>	20

**Table 28** | Evaluation of ligands for Pd-catalyzed amine carbonylation. <sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane. <sup>‡</sup>Reaction conducted by Dr J. Cabrera-Pardo

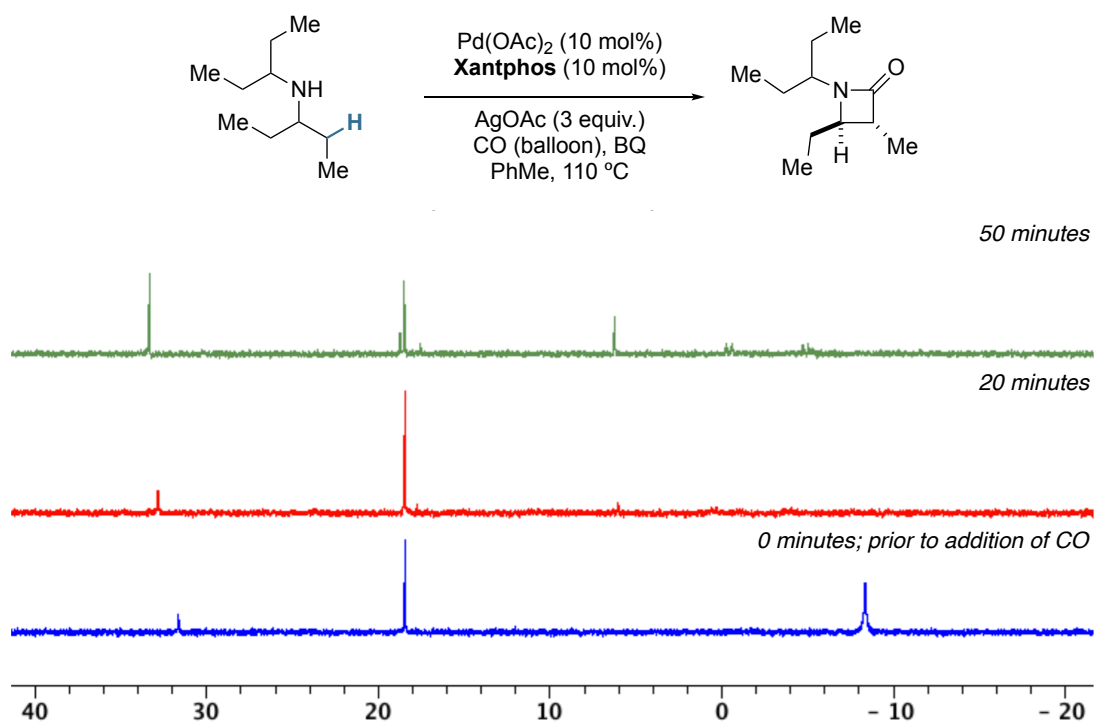


Entry	Additives (mol%)	Yield (%) <sup>a</sup>	Entry	Additives (mol%)	Yield (%) <sup>a</sup>
1 <sup>‡</sup>	$\text{PhCO}_2\text{H}$ (50)	66	5 <sup>‡</sup>	$\text{K}_3\text{PO}_4$ (100)	4
2 <sup>‡</sup>	$\text{AdCO}_2\text{H}$ (50)	67	6 <sup>‡</sup>	$\text{NaOAc}$ (100)	7
3 <sup>‡</sup>	$t\text{-BuCO}_2\text{H}$ (50)	66	7 <sup>‡</sup>	$\text{NaHCO}_3$ (100)	9
4	$\text{CsF}$ (10)	72	8 <sup>‡</sup>	$\text{Cs}_2\text{CO}_3$ (100)	6

**Table 29** | Evaluation of base additives for Pd-catalyzed amine carbonylation. <sup>a</sup>Yields determined by <sup>1</sup>H NMR against internal standard 1,1,2,2-tetrachloroethane. <sup>‡</sup>Reaction conducted by Dr J. Cabrera-Pardo

ii) *Xantphos and Xantphos mono oxide ligand studies*

**Figure 8**  $^{31}\text{P}$   $\{^1\text{H}\}$  NMR (162 MHz,  $d_8$ -PhMe) of Xantphos oxide derivatives: XantPO<sub>2</sub> **517**, Xantphos **485** and XantPO **516**. Measured by Dr J. Cabrera-Pardo.



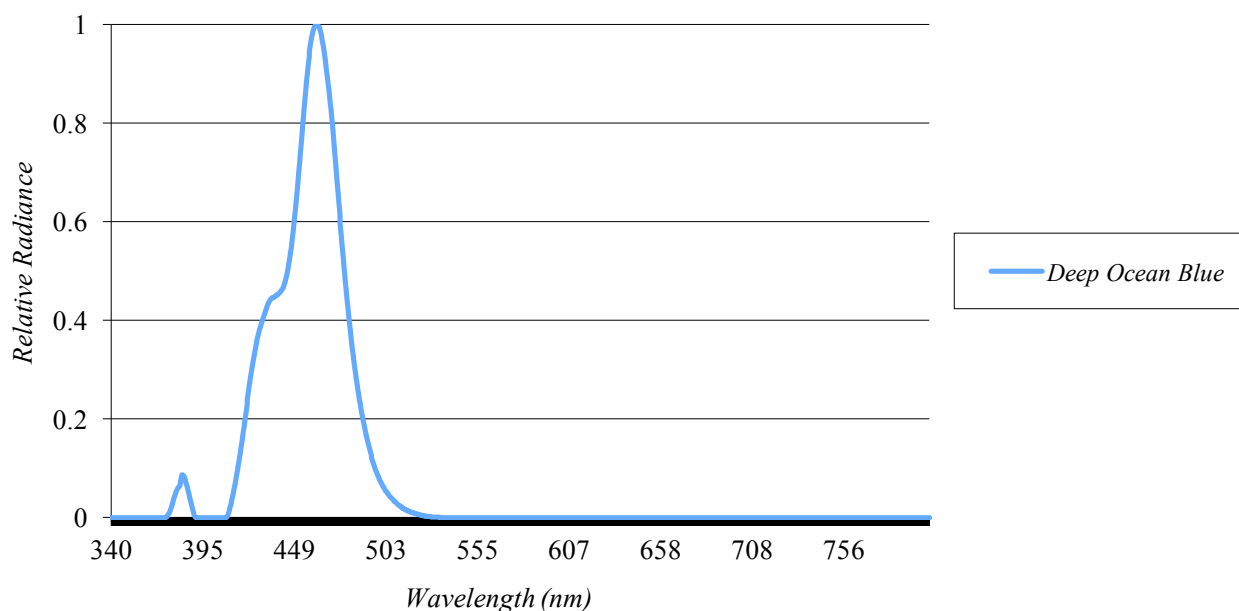
**Figure 9**  $^{31}\text{P}$   $\{^1\text{H}\}$  NMR (162 MHz,  $d_8$ -PhMe) time point study for Pd-catalyzed carbonylation of **492**. Measured by Dr J. Cabrera-Pardo



The  $^{31}\text{P}$  NMR shows major species at  $-8$  ppm prior to the addition of CO and start of the reaction is most likely unbound Xantphos **485**. Notably, this peak rapidly disappears upon heating. The resonance at 19 ppm is consistent with similar reported chemical shifts for  $\text{Pd-P}^{467}$ . Interestingly, this peak diminishes over time with the concomitant growth of the resonance at ca. 33 ppm, which is attributed to  $\text{XantPO}_2 \text{P=O-Pd}^{467}$ . The resonance at 7 ppm bears similarity to neutral *trans*-spanning (xantphos) $\text{Pd}^{\text{II}}$  complexes<sup>646</sup>. Two minor resonances can be observed as doublets at ca. 0 ppm and  $-5$  ppm which that tentatively be ascribed to the electron-rich mono- or bis-(amine) $\text{Pd}^0(\text{xantphos})$  complex<sup>465</sup>.

### iii) Photophysical studies

#### A160WE Tuna Blue Spectrum



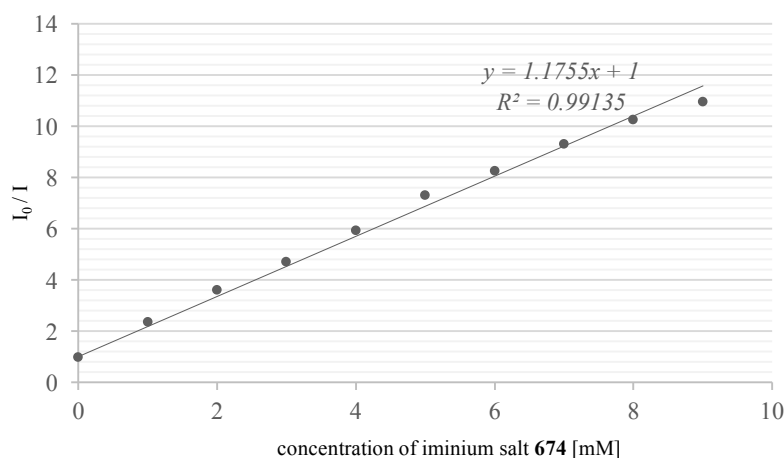
**Figure 10** | Emission spectrum for Kessil A160WE Tuna Blue lamp. Data kindly provided by Kessil.

### Stern Volmer Quenching Studies

Emission intensities were recorded using a Shimadzu RF-6000 spectrofluorometer. Experiments were recorded using a quartz cell equipped with septa-lined screw cap under Ar. All *fac*- $\text{Ir}(\text{ppy})_3$  solutions were excited at 320 nm and the emission intensity recorded at 518 nm. The iminium ion **674** was weighed in a glove box and a stock solution formed in anhydrous degassed dichloromethane and stored in a Schlenk tube. The appropriate amount of *fac*- $\text{Ir}(\text{ppy})_3$ , as a solution in anhydrous degassed dichloromethane, and iminium ion **674** was added to the dry quartz cell equipped with

septa-lined screw cap under Ar and the emission spectra collected. The emission of each concentration was recorded 5 times and an average was taken.

*Stern Volmer quenching of Ir(ppy)<sub>3</sub> by iminium salt 674*



**Figure 6** | Stern Volmer quenching study recording emission intensities of fac-Ir(ppy)<sub>3</sub> ( $c = 10 \mu\text{M}$  in dichloromethane) with varying concentration of iminium salt **674**

Quenching coefficient calculated according to Chen<sup>559</sup> (equation 1):

$$\text{Stern Volmer equation: } F_0/F = 1 + k_q\tau_0[Q]$$

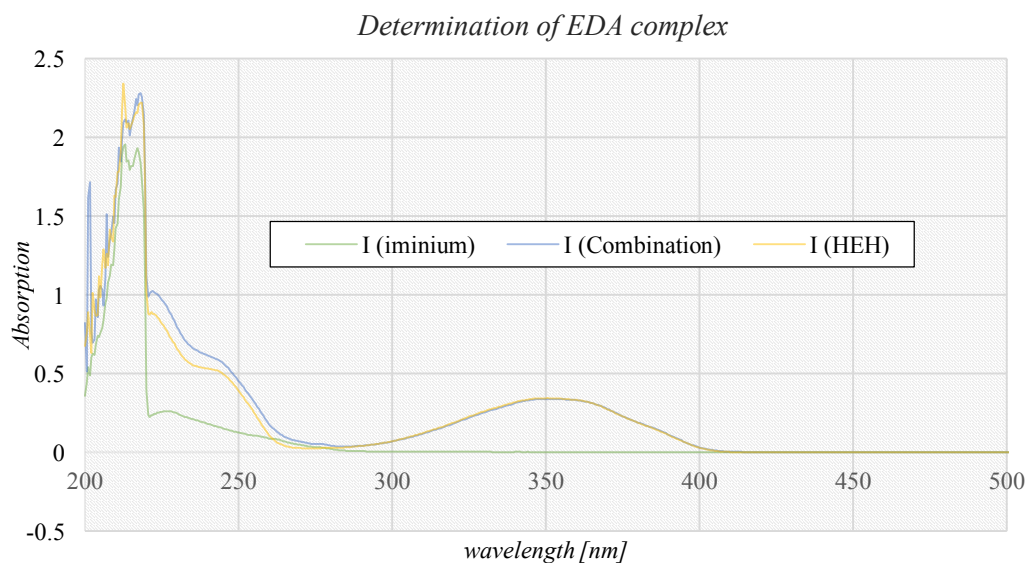
$$k_q\tau_0 = 1.176 \text{ L.mol}^{-1}$$

$$\tau_0 = 1.9 \mu\text{s}$$

$$k_q = 6.2 \times 10^5 \text{ L.mol}^{-1}\text{s}^{-1}$$

### UV-Vis Studies

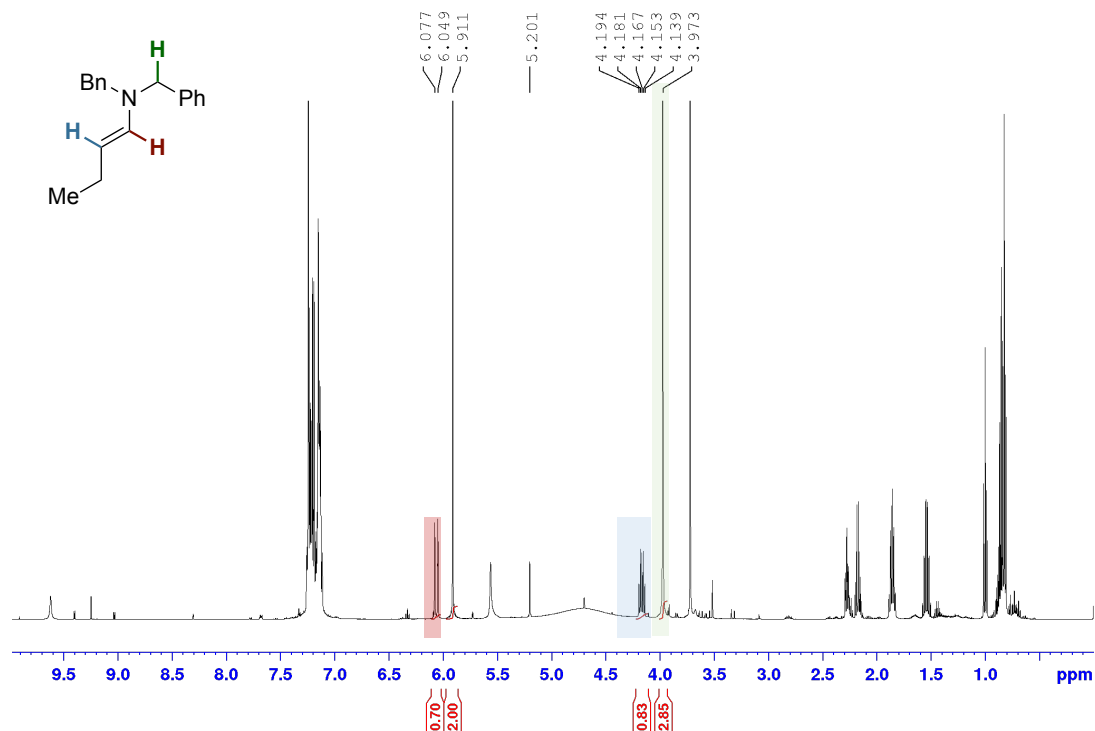
UV-Vis analysis was performed on a Shimadzu UV-1800 spectrophotometer. Experiments were recorded using a quartz cell equipped with septa-lined screw cap under Ar. In a typical experiment, the iminium salt was weighed in a glove box and a stock solution formed in anhydrous degassed dichloromethane and stored in a Schlenk tube (2 mM). The appropriate amount of Hantzsch ester **126**, as a solution in anhydrous degassed dichloromethane (2 mM), and iminium ion **674** was added to the dry quartz cell equipped with septa-lined screw cap under Ar and made up to a total volume of 3.5 mL with anhydrous degassed dichloromethane (0.057 mM). The presence of an electron donor-acceptor (EDA) complex was not observed.



**Figure 11** | UV-Vis studies of iminium salt **674** and Hantzsch ester **126**.

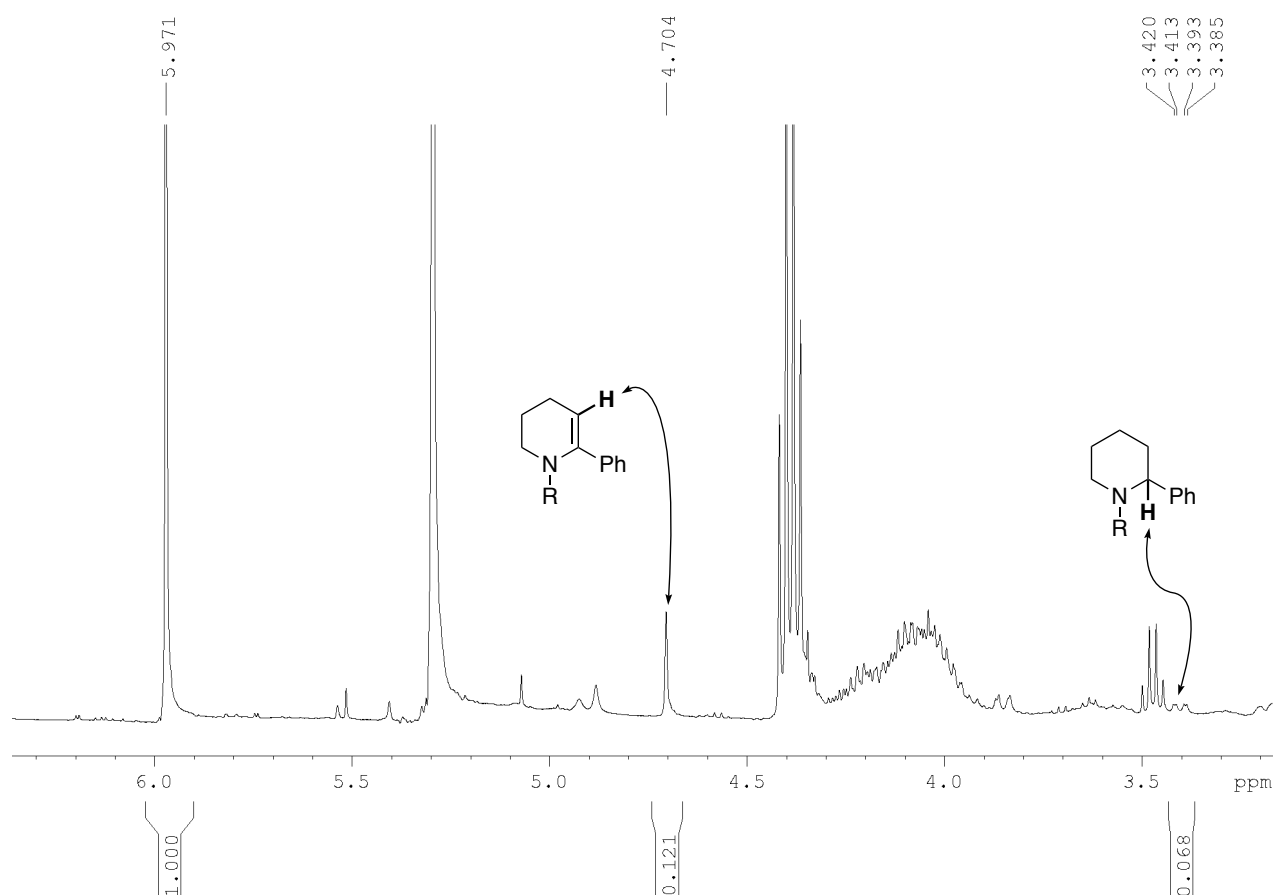
iv) *Photoredox NMR studies*

$^1\text{H}$  NMR study of the reaction mixture ( $\text{Bn}_2\text{NH}$ , butyraldehyde **674** and 20 mol% propionic acid) measured after 5 minutes; 85% enamine **658** formation against internal standard.



**Figure 11** |  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ ) of crude reaction mixture measured against 1,1,2,2-tetrachloroethane internal standard

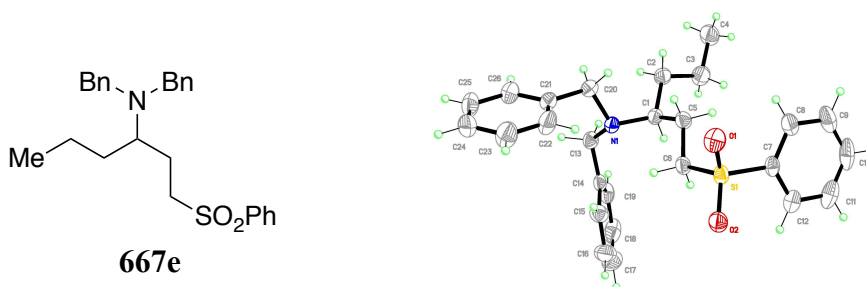
$^1\text{H}$  NMR study of photocatalytic reductive alkylation using 2-phenylpiperidine **671s**, butryaldehyde and *n*-butyl acrylate under standard conditions.



**Figure 12** | Crude  $^1\text{H}$  NMR analysis of the photoredox mediated reductive alkylation of 2-phenylpiperidine, butryaldehyde and *n*-butyl acrylate against internal standard 1,1,2,2-tetrachloroethane.

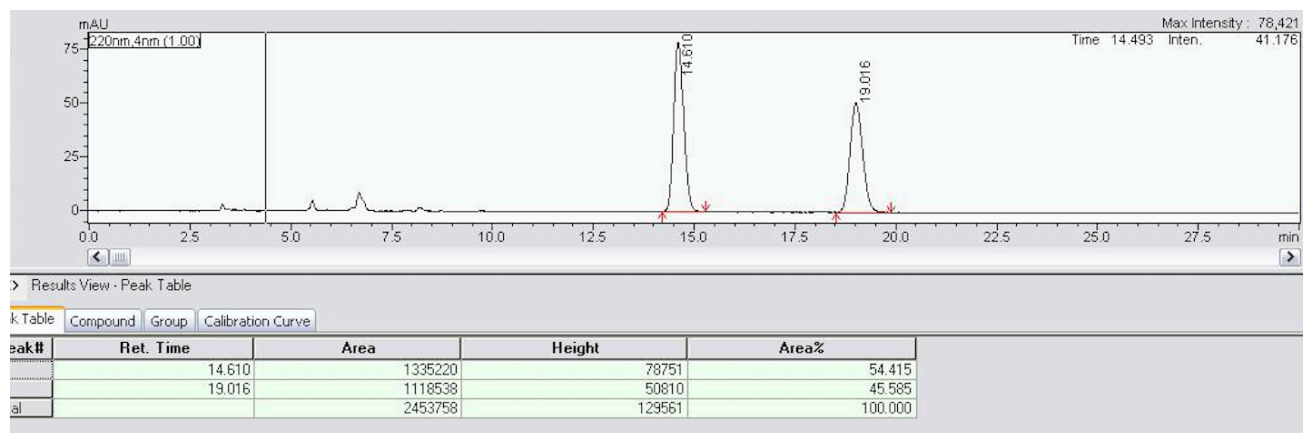
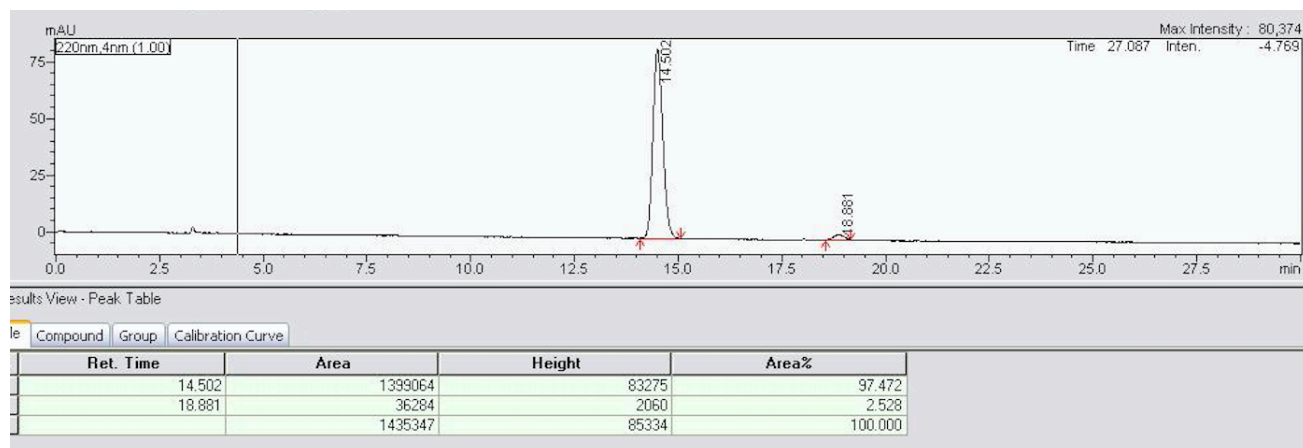
Saturated amine **672s** product compared against authentic sample. Putative enamine **672s'**  $\text{N}(\text{Ph})\text{C}=\text{C}-\text{H}$  resonance determined by analogy to literature compounds<sup>647</sup>.

## v) X-ray crystallographic data



Identification code	MG_B2_0035	
Empirical formula	C <sub>26</sub> H <sub>31</sub> NO <sub>2</sub> S	
Formula weight	421.58	
Temperature	180(2) K	
Wavelength	1.54178 Å	
Crystal system	monoclinic	
Space group	P2 <sub>1</sub> /n	
Unit cell dimensions	a = 11.5839(3)	α = 90°
	b = 15.2860(4)	β = 95.6920(10)°
	c = 13.2865(3)	γ = 90°
Volume	2341.06(10)	
Z	4	
Density (calculated)	1.196 g/cm <sup>3</sup>	
Absorption coefficient (μ)	1.385 mm <sup>-1</sup>	
F (000)	904	
Crystal size	0.500 x 0.350 x 0.830 mm <sup>3</sup>	
θ range for data collection	4.421 to 66.623°	
Index ranges	-13 ≤ h ≤ 12, -18 ≤ k ≤ 17, -15 ≤ l ≤ 15	
Reflections collected	28882	
Independent reflections	4121 [R(int) = 0.0420]	
Completeness to θ	66.623° = 100.00%	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7528 and 0.5279	
Refinement method	Full-matrix least-squares F <sup>2</sup>	
Data / restraints / parameters	4121 / 0 / 272	
Goodness-of-fit on F <sup>2</sup>	1.052	
Final R indices [I > 2σ(I)]	R1 = 0.0349, wR2 = 0.0845	
R indices (all data)	R1 = 0.0390, wR2 = 0.0878	
Absolute structure parameter	0	
Largest diff. peak and hole	0.277 and -0.371 eÅ <sup>-3</sup>	

## vi) Chiral HPLC traces

*(S)*-2-(*tert*-butyl)-3-Cbz-4-methyleneoxazolidin-5-one **668***Racemic Trace**Enantioenriched trace*

## **Appendix III**

### *Published Work*

## C–H Activation

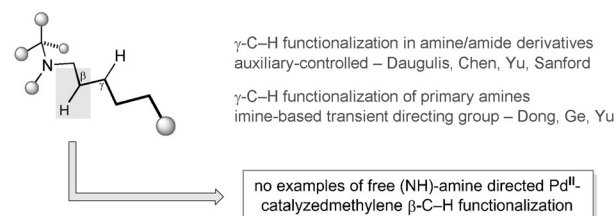
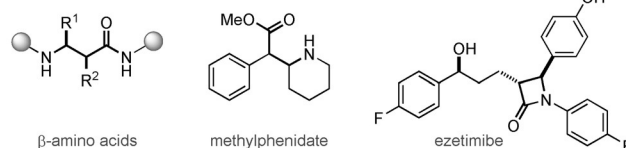
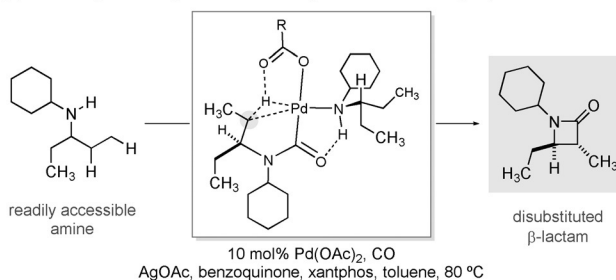
International Edition: DOI: 10.1002/anie.201706303  
German Edition: DOI: 10.1002/ange.201706303Selective Palladium(II)-Catalyzed Carbonylation of Methylene  $\beta$ -C–H Bonds in Aliphatic Amines

Jaime R. Cabrera-Pardo, Aaron Trowbridge, Manuel Nappi, Kyohei Ozaki, and Matthew J. Gaunt\*

**Abstract:** Palladium(II)-catalyzed C–H carbonylation reactions of methylene C–H bonds in secondary aliphatic amines lead to the formation of *trans*-disubstituted  $\beta$ -lactams in excellent yields and selectivities. The generality of the C–H carbonylation process is aided by the action of xantphos-based ligands and is important in securing good yields for the  $\beta$ -lactam products.

One of the most important developments in synthetic chemistry over the last 20 years has been the advent of transition-metal-catalyzed C–H activation reactions.<sup>[1]</sup> While the majority of these successful catalytic processes exploit the functionalization of C(sp<sup>2</sup>)–H bonds, embracing C(sp<sup>3</sup>)–H bonds as reactive entities remains a challenge to synthetic chemists and continues to inspire intensive efforts.<sup>[2]</sup> Arguably, the most successful approaches to C(sp<sup>3</sup>)–H functionalization have exploited processes based on functional-group-directed C–H cleavage at methyl groups with electrophilic palladium(II) catalysts.<sup>[3]</sup> Despite this, selective Pd-catalyzed C–H functionalization at methylene sites remains particularly challenging because the increased steric interactions that result from engaging a mid-chain C–H bond can preclude proximity-driven palladation. Although successful examples of Pd-catalyzed methylene activation usually require the appendage of an auxiliary directing group to facilitate the C–H bond cleavage, these advances have led to a range of novel transformations across a variety of substrate classes.<sup>[4,5]</sup> In contrast, the use of native directing groups to achieve related methylene C–H processes is less common.<sup>[6,7]</sup> Given the prevalence of amines in biologically active molecules,<sup>[8]</sup> we reasoned that a general strategy enabling the selective activation of methylene C–H bonds directed by an intrinsic unprotected amine functional group would be of substantial utility in synthesis.

With respect to previous work on methylene C–H activation, the groups of Daugulis,<sup>[4a]</sup> Chen,<sup>[4b]</sup> Yu,<sup>[4f,7b]</sup> and Sanford<sup>[4g]</sup> have reported directed transformations with a range of aliphatic amine derivatives (Scheme 1 a). Each of these processes, however, requires the use of a preinstalled auxiliary group to enable functionalization, and additional, often complicated steps are always needed for its processing.

(a) State of the art in amine-directed methylene C–H functionalization with Pd<sup>II</sup>(b)  $\beta$ -Functionality is a common feature in biologically relevant aliphatic amines(c) Pd<sup>II</sup>-catalyzed methylene C–H carbonylation of secondary aliphatic amines

**Scheme 1.** Evolution of methylene  $\beta$ -C–H activation in aliphatic amines.

More recently, the groups of Dong,<sup>[7a]</sup> Yu,<sup>[7b]</sup> and Ge<sup>[7c]</sup> have reported that transiently formed catalytic auxiliaries (via imines) can be applied to methylene C–H activation in some functionally simple primary amines. In most of the aforementioned cases, auxiliary-controlled methylene C–H activation takes place at the  $\gamma$ -position to the amine by “classical” five-membered-ring cyclopalladation. To the best of our knowledge, there is no direct functionalization process that selectively targets a methylene C–H bond in the  $\beta$ -position to an unprotected aliphatic amine;<sup>[9,10]</sup> such a transformation would give rise to a structural feature that is ubiquitous in biologically relevant complex amines (Scheme 1 b).

Herein, we report a general process for the Pd-catalyzed functionalization of methylene C–H bonds at the  $\beta$ -position to an unprotected aliphatic amine that does not require an auxiliary group. By exploiting a novel carbonylation pathway, precluding classical cyclopalladation, the C–H functionalization process inserts CO between the  $\beta$ -carbon atom and the amine to selectively afford *trans*-disubstituted  $\beta$ -lactams

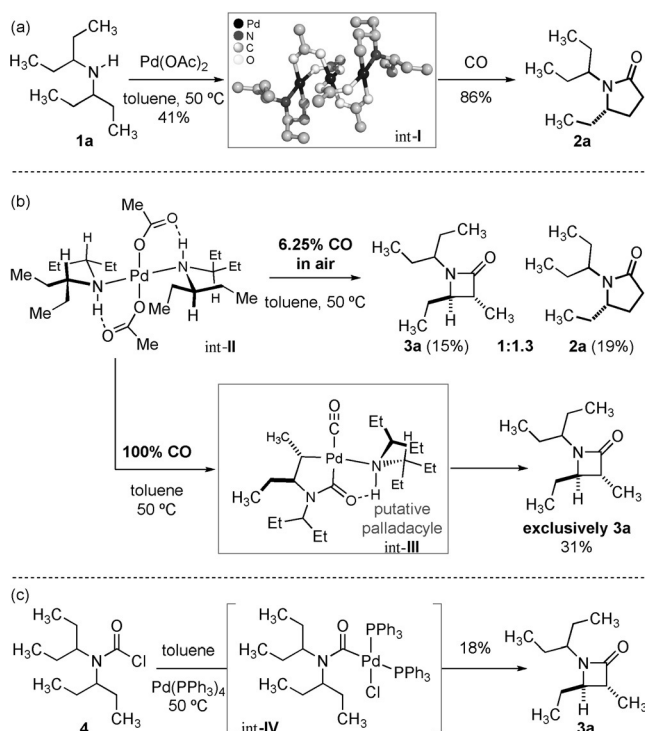
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Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:  
<https://doi.org/10.1002/anie.201706303>.



(Scheme 1c). The operationally simple reaction produces  $\beta$ -lactams in good yields and works for a wide range of functionally diverse and readily available amines. We believe that the versatile  $\beta$ -lactam products will be of significant interest to practitioners of synthetic and medicinal chemistry.

First, we benchmarked the C–H activation step by treating amine **1a** with a stoichiometric amount of  $\text{Pd}(\text{OAc})_2$ . We found that **1a** underwent classical cyclopalladation at the  $\gamma$ -C–H bond to form the five-membered-ring complex, int-I (Scheme 2a).<sup>[11]</sup> When this complex was stirred under an



**Scheme 2.** Preliminary mechanistic experiments.

atmosphere of CO, the expected  $\gamma$ -lactam **2a** was formed. The pathway to **2a** (via int-I) is consistent with cyclopalladation followed by CO insertion and reductive elimination.<sup>[3h,i,12]</sup> Next, we stirred a mixture of (bis)amine  $\text{Pd}^{\text{II}}$  complex int-II (an established precursor to C–H activation)<sup>[3h]</sup> under 1 atm of CO/air. We were surprised to find that the reaction afforded a 1.3:1 mixture of  $\gamma$ -lactam **2a** and  $\beta$ -lactam **3a**, the latter arising from methylene  $\beta$ -C–H carbonylation (Scheme 2b). We postulated that **3a** could be formed via a competitive C–H carbonylation pathway, recently outlined by our laboratory.<sup>[13]</sup> If CO is first activated by the  $\text{Pd}(\text{OAc})_2$ , it could engage the amine to form a carbamoyl  $\text{Pd}^{\text{II}}$  species, from which C–H activation can occur at the  $\beta$ -methylene position via a five-membered-ring transition state (Scheme 1c); reductive elimination from putative palladacycle int-III would form  $\beta$ -lactam **3a**. Notably, the concentration of CO appears to control the pathway of the C–H carbonylation process; only **3a** is observed when int-II is stirred under a pure CO atmosphere. The proposed pathway to **3a** is further supported by reaction of carbamoyl chloride **4** with  $\text{Pd}(\text{PPh}_3)_4$ , which presumably passes through a related carba-

moyl  $\text{Pd}^{\text{II}}$  intermediate (int-IV) towards the  $\beta$ -lactam (Scheme 2c).<sup>[10a,13,14]</sup>

Using amine **1a**, we assessed a catalytic methylene  $\beta$ -C–H carbonylation by testing the reaction conditions that had been successful for our methyl  $\beta$ -C–H carbonylation.<sup>[13]</sup> Although the reaction produced **3a** in a capricious 23 % assay yield, a significant amount of N-acetylated amine side product (28 %) was observed.  $\text{Cu}^{\text{II}}$  salts are known to catalyze N acetylation,<sup>[15]</sup> but we found that changing the oxidant from  $\text{Cu}(\text{OAc})_2$  to  $\text{AgOAc}$  increased the yield of **3a** to 42 %, and reduced the amount of acetylated side product (Table 1, entry 1).

**Table 1:** Selected optimization.<sup>[a]</sup>

Entry	Catalyst	AgX	BQ [equiv]	Ligand	Yield [%] (d.r.)
1	$\text{Pd}(\text{OAc})_2$	$\text{AgOAc}$	2	Li-quinoline	42 (12:1)
2	$\text{Pd}(\text{OAc})_2$	$\text{AgOAc}$	2	$\text{PPh}_3$	28 (12:1)
3	$\text{Pd}(\text{OAc})_2$	$\text{AgOAc}$	2	xantphos	82 (12:1)
4	$\text{Pd}(\text{OAc})_2$	$\text{AgOPiv}$	2	xantphos	54 (12:1)
5	$\text{Pd}(\text{OAc})_2$	$\text{AgOBz}$	2	xantphos	74 (12:1)
6	$\text{Pd}(\text{OAc})_2$	$\text{AgOAc}$	–	xantphos	0
7	–	$\text{AgOAc}$	2	xantphos	0
8	$\text{Pd}(\text{OAc})_2$	–	2	xantphos	0
9	$\text{Pd}(\text{OAc})_2$	$\text{AgOAc}$	2	–	23 (12:1)
10	$\text{Pd}(\text{OAc})_2$	$\text{AgOAc}$	2	xantphosO	80 (12:1)
11	$\text{Pd}(\text{OAc})_2$	$\text{AgOAc}$	2	xantphos(O) <sub>2</sub>	23 (12:1)

[a] Yields and diastereomeric ratios (d.r.) determined by  $^1\text{H}$  NMR analysis with 1,1,2,2-tetrachloroethane as internal standard.

Prompted by the observation that a reaction using  $\text{PPh}_3$  as the ligand (instead of Li-quinoline) also formed **3a** (entry 2), we examined a series of phosphines and found that the use of bidentate xantphos gave an excellent yield of **3a** (entry 3).<sup>[16]</sup> The reaction of **1a** also worked well using different silver carboxylates (entries 3–5). Control experiments highlighted the essential roles of BQ as well as the  $\text{Pd}^{\text{II}}$  and  $\text{Ag}^{\text{I}}$  carboxylates (entries 6–8). The optimal conditions involved the treatment of amine **1a** with 10 mol % of  $\text{Pd}(\text{OAc})_2$ , 10 mol % of xantphos, 3 equiv of  $\text{AgOAc}$ , and 2 equiv of BQ under CO (1 atm) at 80 °C in toluene; product **3a** was then isolated in 82 % yield. Interestingly, we found that the reaction of **1a** using CO diluted with air (see Scheme 2b) under otherwise identical reaction conditions resulted in the formation of the  $\beta$ - and  $\gamma$ -lactams in a 3:1 ratio, further supporting the dependence of the pathway on CO concentration. The successful use of phosphines in oxidative C–H carbonylation is surprising given their propensity towards oxidation to phosphine oxides; the unique effect of xantphos, compared to other phosphines, is also striking. Accordingly, we found that a reaction using xantphos monooxide gave almost the same yield as the use of xantphos (entry 10);<sup>[17a,b]</sup> however, the yield dropped dramatically when xantphos dioxide was used (entry 11).<sup>[16]</sup> While we are unsure of its precise role, we believe that xantphos (or its monooxide) most

**Table 2:** Scope of the methylene C–H carbonylation.

<p>(a)</p> <p><b>3b</b>, 73%, 20:1 d.r.</p> <p><b>3c</b>, 67%, 12:1 d.r.</p> <p><b>3d</b>, 51%, 7:1 d.r.</p> <p><b>3e</b>, 82%, 10:1 d.r.<sup>[a]</sup></p> <p><b>3f</b>, 75%, &gt;20:1 d.r.<sup>[a]</sup></p> <p><b>3g</b>, 59%, 20:1 d.r.<sup>[b]</sup></p> <p><b>3h</b>, 60%, 12:1 d.r.</p> <p><b>3i</b>, 48%, 20:1 d.r.<sup>[a,b]</sup></p> <p><b>3j</b>, 60%, 12:1 d.r.<sup>[a,b]</sup></p> <p><b>3k</b>, 64%, &gt;20:1 d.r.<sup>[a]</sup></p> <p><b>3l</b>, 75%, &gt;20:1 d.r., gram scale<sup>[a]</sup></p> <p><b>3m</b>, 61%, 20:1 d.r.<sup>[b]</sup></p> <p><b>3n</b>, 85%, 15:1 d.r.</p> <p><b>3o</b>, 67%, 15:1 d.r.<sup>[a]</sup></p> <p><b>3p</b>, 80%, 12:1 d.r.<sup>[a]</sup></p> <p><b>3q</b>, 40%, &gt;20:1 d.r.<sup>[a]</sup></p> <p><b>3r</b>, 78%, 9:1 d.r.<sup>[a]</sup></p> <p><b>3s</b>, 60%, &gt;20:1 d.r.<sup>[a]</sup></p> <p><b>3t</b>, 52%, &gt;20:1 d.r.</p> <p><b>3u</b>, 81%, &gt;20:1 d.r.</p> <p><b>3v</b>, 65%, &gt;20:1 d.r.</p> <p><b>3w</b>, 72%, &gt;20:1 d.r.</p> <p><b>3x</b>, 51%, &gt;20:1 d.r.<sup>[a]</sup></p> <p><b>3y</b>, 62%, 12:1 d.r.</p> <p><b>3z</b>, 62%, 12:1 d.r.</p> <p><b>3aa</b>, 66%</p> <p><b>3ab</b>, 51%</p> <p><b>3ac</b>, 61%, 15:1 d.r.</p> <p><b>3ad</b>, 60%, &gt;20:1 d.r.</p> <p><b>3ae</b>, 63%, 15:1 d.r.</p>	
<p>(b)</p> <p><b>3u</b>, 81%, &gt;20:1 d.r.</p> <p><b>3v</b>, 65%, &gt;20:1 d.r.</p> <p><b>3w</b>, 72%, &gt;20:1 d.r.</p> <p><b>3x</b>, 51%, &gt;20:1 d.r.<sup>[a]</sup></p> <p><b>3y</b>, 62%, 12:1 d.r.</p> <p><b>3z</b>, 62%, 12:1 d.r.</p> <p><b>3aa</b>, 66%</p> <p><b>3ab</b>, 51%</p> <p><b>3ac</b>, 61%, 15:1 d.r.</p> <p><b>3ad</b>, 60%, &gt;20:1 d.r.</p> <p><b>3ae</b>, 63%, 15:1 d.r.</p>	

[a] With Pd(OPiv)<sub>2</sub> (10 mol%), AgOPiv (3 equiv). [b] Product exists as a 1:1 mixture of diastereomers, each with diastereoselectivity across the  $\beta$ -lactam as stated.

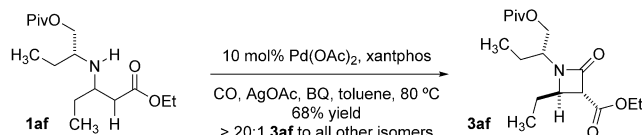
likely stabilizes Pd<sup>0</sup> at the end of the catalytic cycle prior to oxidation to the Pd<sup>II</sup> species required for the reaction.<sup>[17c]</sup>

With optimized reaction conditions in hand, we examined the scope of the methylene  $\beta$ -C–H carbonylation process. As shown in Table 2, structurally and functionally diverse amines undergo efficient  $\beta$ -C–H carbonylation to *trans*-disubstituted  $\beta$ -lactams. Branching at the  $\alpha$ - and  $\beta$ -carbon atoms on the non-reacting side of the amine is well tolerated to provide the  $\beta$ -lactams in good yields (**3a–3f**). Interestingly, we found that the use of hindered carboxylate ligands was required for amines not containing  $\alpha$ -branching to prevent the formation of the undesired N acetylation side products. A variety of functional groups, including alkene, ester, arene, and oxetane moieties, can be accommodated by the reaction, and the corresponding  $\beta$ -lactams were formed in good yields (**3g–3p**). Among these, we note that a) a thioether motif neither deactivates the catalyst nor succumbs to oxidation, and  $\beta$ -lactam **3h** is produced in high yield, b) the free NH  $\beta$ -

lactam can be obtained through photochemical cleavage of an *N*-benzyl derivative,<sup>[18]</sup> and c) the reaction was amenable to being performed on gram scale (**3l**). Linear substituents can be incorporated on the non-reacting side of the amine (**3q–3t**), and we observed that the carbonylation is tolerant of Lewis basic heteroarenes (**3s** and **3t**), thereby enhancing the utility of this process towards medicinal chemistry applications.<sup>[8,19]</sup> A range of functional groups can also be included on the reacting side of the amine (Table 2b, **3u–3ae**). Substrates derived from protected amino alcohols worked well to provide functionalized  $\beta$ -lactams in good yields and diastereoselectivities (**3w–3z**); interestingly, C–H carbonylation is not observed at the  $\beta$ -position bearing the O substituent, thereby conveying useful selectivity in more heavily functionalized systems. Selective carbonylation at the benzylic position in phenylalanine- and tryptophan-derived substrates gave highly functionalized  $\alpha$ -aryl- $\beta$ -hydroxymethyl- $\beta$ -lactams (**3y** and **3z**); importantly, no competitive C(sp<sup>2</sup>)–H carbon-

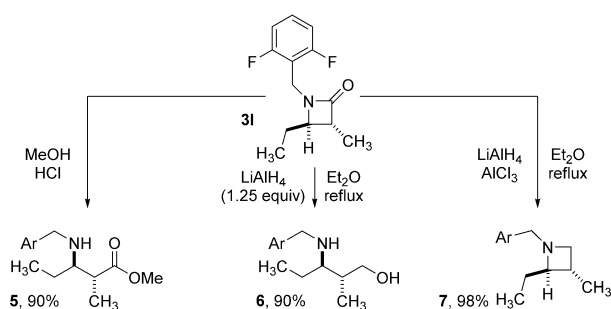
ylation was observed in these  $\beta$ -arene-containing amines. Unfortunately, reaction was not observed when the amine was unbranched on the reacting side;<sup>[16]</sup> however, C–H carbonylation onto cycloalkanes worked well to reveal a useful class of fused-ring  $\beta$ -lactams (**3aa** and **ab**). A selection of heteroarenes on the reacting side of the amine are compatible with the C–H carbonylation (**3ac–3ae**).

To test the limits of the selectivity in this C–H carbonylation, we prepared **1af**, wherein four different  $\beta$ -C–H bonds are accessible to the palladium carboxamide activation (Scheme 3). Remarkably, the reaction selectively occurred at one C–H bond (next to the ester, possibly reflecting C–H acidity or the importance of a Pd enolate) to form **3af**.



**Scheme 3.** Regioselective C–H carbonylation.

The  $\beta$ -lactams could be readily transformed into useful building blocks. Acidic methanolysis formed the  $\beta$ -amino ester **5**, exhaustive reduction afforded the amino alcohol **6**, and treatment with alane delivered the azetidine **7** (Scheme 4).



**Scheme 4.** Derivatization of  $\beta$ -lactams.

In conclusion, we have developed a method for the C–H carbonylation of methylene  $\beta$ -C–H bonds in secondary aliphatic amines to form *trans*-disubstituted  $\beta$ -lactams. We believe that the reaction proceeds via a carbamoyl palladium-(II) intermediate, from which C–H activation is selective for the  $\beta$ -C–H bond via a five-membered-ring cyclopalladation intermediate. The bis(phosphine) xantphos was important for obtaining the  $\beta$ -lactams in high yields. Given the broad tolerance of this reaction to useful functional groups, we believe that this C–H carbonylation process will be of significant interest to practitioners of synthesis and medicinal chemistry.<sup>[8,19]</sup>

## Acknowledgements

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for supporting this research (M.J.G.). We also thank the Marie Curie Foundation (J.R.C.-P. and M.N.) and the Herchel Smith Foundation (A.T.) for funding. Mass spectrometry data were acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

## Conflict of interest

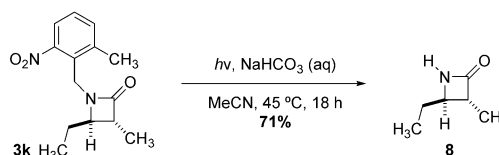
The authors declare no conflict of interest.

**Keywords:** aliphatic amines · carbonylation · C–H activation · lactams · palladium catalysis

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*Angew. Chem.* **2017**, *129*, 12120–12124

- [1] For selected reviews on C(sp<sup>2</sup>)–H activation, see: a) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; *Angew. Chem.* **2012**, *124*, 9092; b) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740.
- [2] For selected reviews on C(sp<sup>3</sup>)–H activation, see: a) O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902; b) N. Dastbaravardeh, M. Christakakou, M. Haider, M. Schnürch, *Synthesis* **2014**, 1421; c) J. He, M. Wasa, K. S. L. Chan, Q. Shao, J.-Q. Yu, *Chem. Rev.* **2017**, *117*, 8754; d) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417.
- [3] For representative examples of directed palladium-catalyzed C–H functionalization at unactivated methyl groups, see: oximes: a) L. V. Desai, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 9542; oxazolines: b) R. Giri, X. Chen, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2005**, *44*, 2112; *Angew. Chem.* **2005**, *117*, 2150; carboxylic acids: c) R. Giri, N. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunderson, J.-Q. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510; methyl hydroxamic acids: d) D.-H. Wang, M. Wasa, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 7190; *N*-aryl carboxamides: e) M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 9886; hydroxy derivatives: f) Z. Ren, F. Mo, G. Dong, *J. Am. Chem. Soc.* **2012**, *134*, 16991; sulfonamides: g) K. S. L. Chan, M. Wasa, L. Chu, B. N. Laforteza, M. Miura, J.-Q. Yu, *Nat. Chem.* **2014**, *6*, 146; free amines: h) A. McNally, B. Haffemayer, B. S. L. Collins, M. J. Gaunt, *Nature* **2014**, *510*, 129; i) J. Calleja, D. Pla, T. W. Gorman, V. Domingo, B. Haffemayer, M. J. Gaunt, *Nat. Chem.* **2015**, *7*, 1009; for a comprehensive review, see also Ref. [2c].
- [4] For auxiliary-controlled palladium-catalyzed methylene functionalization at unactivated C–H bonds, see: pyridine/quinoline-derived amides: a) V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154; b) G. He, G. Chen, *Angew. Chem. Int. Ed.* **2011**, *50*, 5192; *Angew. Chem.* **2011**, *123*, 5298; *N*-aryl carboxamides: c) M. Wasa, K. S. L. Chan, X.-G. Zhang, J. He, M. Miura, J.-Q. Yu, *J. Am. Chem. Soc.* **2012**, *134*, 18570; d) G. Chen, W. Gong, Z. Zhuang, M. S. Andr , Y.-Q. Chen, X. Hong, Y.-F. Yang, T. Liu, K. N. Houk, J.-Q. Yu, *Science* **2016**, *353*, 1023; e) R.-Y. Zhu, K. Tanaka, G.-C. Li, J. He, H.-Y. Fu, S.-H. Li, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 7067; thiocarbamates: f) J. E. Spangler, Y. Kobayashi, P. Verma, D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 11876; amine derivatives: g) J. J. Topczewski, P. J. Cabrera, N. I. Saper, M. S. Sanford, *Nature* **2016**, *531*, 220; for a comprehensive review, see also Ref. [2c].
- [5] For auxiliary-controlled palladium-catalyzed methylene functionalization at activated C–H bonds, see: *N*-aryl carboxamides, cyclopropyl C–H: a) M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3680; benzylic C–H: b) J. He, S. Li, Y. Deng, H. Fu, B. N. Laforteza, J. E. Spangler, A. Homs, J.-Q. Yu,

- Science* **2014**, *343*, 1216; cyclobutyl C–H: c) K.-J. Xiao, D. W. Lin, M. Miura, R.-Y. Zhu, W. Gong, M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 8138; d) F.-L. Zhang, K. Hong, T.-J. Li, H. Park, J.-Q. Yu, *Science* **2016**, *351*, 252; sulfonamides, cyclopropyl C–H: e) K. S. L. Chan, H.-Y. Fu, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 2042; for a comprehensive review, see also Ref. [2c].
- [6] G. Chen, Z. Zhuang, G. C. Li, T. G. Saint-Denis, Y. Xiao, C. L. Joe, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 1506; *Angew. Chem.* **2017**, *129*, 1528.
- [7] For examples of C–H activation of primary amines using transient directing groups in C(sp<sup>3</sup>)–H activation with Pd<sup>II</sup> catalysts, see: a) Y. Xu, M. C. Young, C. Wang, D. M. Magness, G. Dong, *Angew. Chem. Int. Ed.* **2016**, *55*, 9084; *Angew. Chem.* **2016**, *128*, 9230; b) Y. Wu, Y.-Q. Chen, T. Liu, M. D. Eastgate, J.-Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 14554; c) Y. Liu, H. Ge, *Nat. Chem.* **2017**, *9*, 26.
- [8] S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451.
- [9] For auxiliary-controlled β-C–H activation of amine derivatives, see: a) Z. Huang, C. Wang, G. Dong, *Angew. Chem. Int. Ed.* **2016**, *55*, 5299–5303; *Angew. Chem.* **2016**, *128*, 5385–5389; b) N. Gulia, O. Daugulis, *Angew. Chem. Int. Ed.* **2017**, *56*, 3630–3634; *Angew. Chem.* **2017**, *129*, 3684–3688.
- [10] For examples of indirect methods for proximity-driven C–H activation in the β-position to amine derivatives, see: a) D. Dailler, R. Rocaboy, O. Baudoin, *Angew. Chem. Int. Ed.* **2017**, *56*, 7218–7222; *Angew. Chem.* **2017**, *129*, 7324–7328; b) J. Pedroni, N. Cramer, *Angew. Chem. Int. Ed.* **2015**, *54*, 11826; *Angew. Chem.* **2015**, *127*, 11992; c) A. Millet, P. Larini, E. Clot, O. Baudoin, *Chem. Sci.* **2013**, *4*, 2241.
- [11] A. D. Ryabov, *Chem. Rev.* **1990**, *90*, 403.
- [12] For examples of palladium-catalyzed C(sp<sup>3</sup>)–H carbonylation at methyl groups, see: a) E. J. Yoo, M. Masa, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 17378; b) S. Li, G. Chen, C.-G. Feng, W. Gong, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 5267; c) P.-L. Wang, Y. Li, Y. Wu, C. Li, Q. Lan, X.-S. Wang, *Org. Lett.* **2015**, *17*, 3698; d) C. Wang, L. Zhang, C. Chen, J. Han, Y. Yao, Y. Zhao, *Chem. Sci.* **2015**, *6*, 4610; for examples of C(sp<sup>3</sup>)–H carbonylation at methylene groups, see: e) P. Xie, Y. Xie, B. Qian, H. Zhou, C. Xia, H. Huang, *J. Am. Chem. Soc.* **2012**, *134*, 9902; f) P. Xie, C. Xia, H. Huang, *Org. Lett.* **2013**, *15*, 3370; for a related study on methylene C–H carbonylation, see: g) G. Liao, X.-S. Yin, K. Chen, Q. Zhang, S.-Q. Zhang, B.-F. Shi, *Nat. Commun.* **2016**, *7*, 12901.
- [13] D. Willcox, B. G. N. Chappell, K. F. Hogg, J. Calleja, A. P. Smalley, M. J. Gaunt, *Science* **2016**, *354*, 851.
- [14] C. Tsukano, M. Okuno, Y. Takemoto, *Angew. Chem. Int. Ed.* **2012**, *51*, 2763; *Angew. Chem.* **2012**, *124*, 2817.
- [15] B. López, A. Rodríguez, D. Santos, J. Albert, X. Ariza, J. Garcia, J. Granell, *Chem. Commun.* **2011**, *47*, 1054.
- [16] See the Supporting Information for details.
- [17] a) H. Li, K. M. Belyk, J. Yin, Q. Chen, A. Hyde, Y. Ji, S. Oliver, M. T. Tudge, L.-C. Campeau, K. R. Campos, *J. Am. Chem. Soc.* **2015**, *137*, 13728; b) Y. Ji, R. E. Plata, C. S. Regens, M. Hay, M. Schmidt, T. Razler, Y. Qiu, P. Geng, Y. Hsiao, T. Rosner, M. D. Eastgate, D. G. Blackmond, *J. Am. Chem. Soc.* **2015**, *137*, 13272; c) S. E. Denmark, R. C. Smith, S. A. Tymonko, *Tetrahedron* **2007**, *63*, 5730.
- [18] The nitrobenzyl group was removed by photochemical cleavage.
- [19] For a review on β-lactams, see: B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Rev.* **2007**, *107*, 4437.



- [19] For a review on β-lactams, see: B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Rev.* **2007**, *107*, 4437.

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## The $\alpha$ -tertiary amine motif drives remarkable selectivity for Pd-catalyzed carbonylation of $\beta$ -methylene C–H bonds†

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and Matthew J. Gaunt \*

The selective C–H carbonylation of methylene bonds in the presence of traditionally more reactive methyl C–H and C(sp<sup>2</sup>)–H bonds in  $\alpha$ -tertiary amines is reported. The exceptional selectivity is driven by the bulky  $\alpha$ -tertiary amine motif, which we hypothesise orientates the activating C–H bond proximal to Pd in order to avoid an unfavourable steric clash with a second  $\alpha$ -tertiary amine on the Pd centre, promoting preferential cyclopalladation at the methylene position. The reaction tolerates a range of structurally interesting and synthetically versatile functional groups, delivering the corresponding  $\beta$ -lactam products in good to excellent yields.

Methods that enable the catalytic functionalization of unreactive aliphatic C–H bonds have great potential in streamlining the synthesis of complex molecules such as natural products or medicinal agents.<sup>1</sup> However, these molecules contain many types of C–H bond, each with a subtly different reactivity that is often influenced by an intricate interplay of factors including steric, inductive and conductive effects, and sometimes innate strain.<sup>2</sup> As a result, catalytic processes that target certain C–H bonds are an important goal for chemical synthesis, and one that continues to inspire intense research effort.<sup>3</sup>

Arguably, the most common strategy employed for selective C–H activation involves the use of palladium(II) catalysts, directed to a specific position by a resident polar functional group.<sup>4</sup> Known as cyclopalladation, this activation mode most commonly targets the  $\gamma$ -C–H bond with respect to the directing group, to form a 5-membered ring intermediate from which further reaction takes place to install the new functionality. In most cases, the directing motifs needed to facilitate the C–H activation are bespoke auxiliaries or tailored protecting groups that need to be added to (and removed from) an intrinsic functionality of the parent molecule.<sup>5</sup> While the use of auxiliaries has enabled many types of C–H activations, by contrast, the number of related transformations directed by functional groups that are native to aliphatic molecules (carboxylic acids,

amines, hydroxyl groups) is more limited, despite the emergence of some important recent examples.<sup>6</sup>

Recently, we reported a new activation mode for C–H carbonylation of unprotected aliphatic secondary amines to form tertiary  $\beta$ -lactams.<sup>7</sup> In contrast to other methods, the C–H activation step takes place at the  $\beta$ -C–H bond to the directing nitrogen functionality.<sup>8</sup> This change in selectivity is brought about because the reaction follows a pathway that is distinct from classical cyclopalladation-mediated reactions. Rather than C–H activation preceding the CO insertion step, the new pathway uses an amine bound palladium(II) carboxylate to first engage CO to form a carbamoyl–Pd(II) complex. By virtue of CO already being inserted between the amine and the Pd(II) centre, C–H activation *via* a 5-membered ring transition state now takes place at the  $\beta$ -C–H bond with respect to the resident amine motif. We have shown, firstly, that a wide range of aliphatic amines displaying  $\alpha$ -branched methyl groups undergo  $\beta$ -C–H carbonylation to the corresponding  $\beta$ -lactams.<sup>7</sup> Secondly, we found that in the absence of suitably disposed methyl groups, the C–H carbonylation was able to target the  $\beta$ -methylene C–H bond under slightly modified conditions to form *trans*-disubstituted  $\beta$ -lactams.<sup>9</sup> The functional group tolerance exhibited by both of these C–H carbonylation processes is particularly notable and gives rise to a range of versatile and diverse  $\beta$ -lactam products.

During the course of our studies to further explore this carbonylation platform, we discovered a remarkable feature inherent to this C–H activation mode.  $\alpha$ -Tertiary amines (ATAs) displaying both a  $\beta$ -methyl C–H bond and  $\beta$ -methylene C–H bond undergo exclusive carbonylation at the traditionally less reactive and more hindered methylene position.<sup>10</sup> Central to the success of this selective C–H carbonylation is the presence of

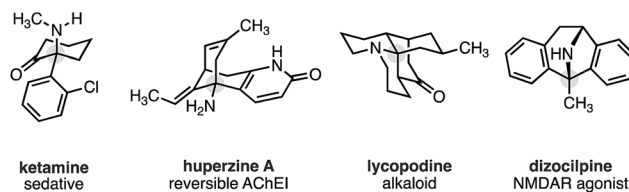
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† Electronic supplementary information (ESI) available: Experimental procedures, characterization data and kinetic details. CCDC 1570476. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7sc03876c

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a fully substituted carbon atom on one side of the amine linkage, which steers the reaction to the C–H bond adjacent to this bulky structural feature (Scheme 1c). Herein, we report the development of a general C–H carbonylation exploiting this selectivity-inducing parameter. The ATA motif is widespread among natural products and pharmaceuticals displaying unique physiochemical properties (Scheme 2).<sup>11</sup> However, due to the limited number of methods available in accessing these compounds, we believe that the direct functionalization of ATAs would provide convenient access to a range of molecular scaffolds that would be attractive to practitioners of synthetic and medicinal chemistry.

Using the conditions developed for methylene C–H carbonylation,<sup>9</sup> using xantphos as a ligand,<sup>12</sup> we first assessed substrates displaying a variety of substituents in the  $\alpha$ -position on the reacting side of the amine linkage; the secondary amines also contained a  $\beta$ -methyl C–H bond (in the form of an *N*-ethyl group) on the other side of the free (NH) motif (Table 1). Substrates containing protected  $\alpha$ -hydroxymethylene substituents proved effective under the reaction conditions, delivering the fused bicyclic  $\beta$ -lactams (**2a** and **2b**) resulting from selective methylene

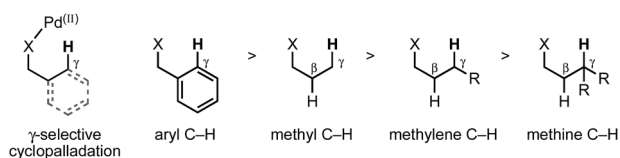
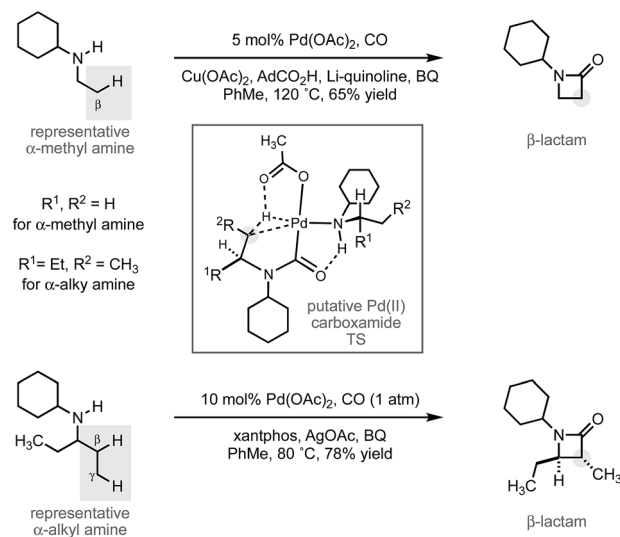
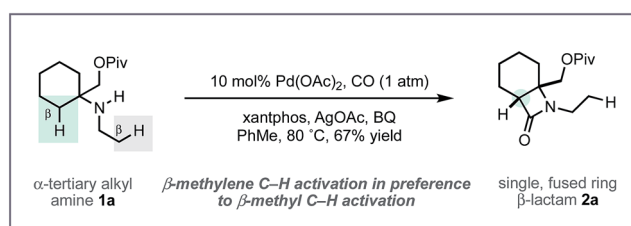


Scheme 2 Pharmaceuticals and alkaloids containing the ATA motif.

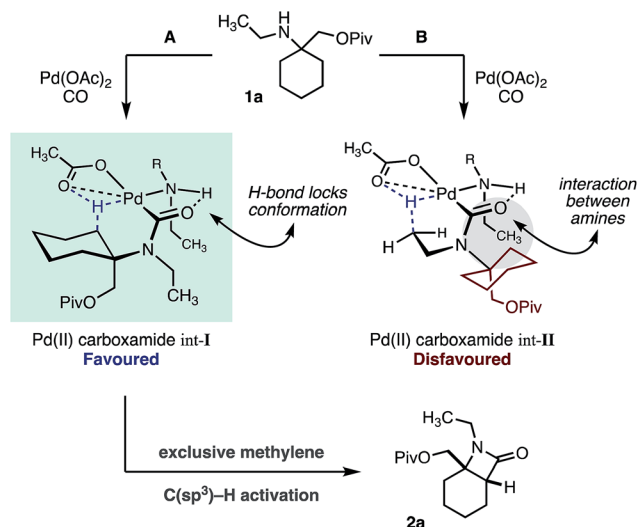
C–H carbonylation in good yields.<sup>13</sup> Moreover, an  $\alpha$ -*n*-butyl chain was also sufficient to deliver the corresponding bicyclic  $\beta$ -lactam **2c** in 59% yield, remarkably without any activation of the exocyclic  $\alpha$ -alkyl substituent, which contains a competitive methylene  $\beta$ -C–H bond. Exclusive methylene C–H activation also occurred on the corresponding acyclic substrate **1d**, further expanding the utility of the methodology. The corresponding *N*-isopropyl substrate **1e**, for which there is a 6 : 4 ratio of methyl to methylene C–H bonds, afforded a 1.5 : 1 mixture of  $\beta$ -lactams in favour of the methylene C–H activated product, exemplifying the remarkable selectivity inherent to this C–H activation process.

We hypothesize that the selectivity of this methylene C–H carbonylation process arises from the unique Pd(II)–carboxamide intermediate (pathways A and B, Scheme 3). Based on our previous work,<sup>7</sup> we propose that a key hydrogen-bond between the carboxamide carbonyl and ligated amine locks the relative conformation of these two substituents, in turn generating two potentially reactive carboxamide intermediates (int-I and int-II). We believe that the large  $\alpha$ -tertiary amine substituent generates an unfavorable steric clash with the ligated amine (int-II), resulting in preferential activation of the highlighted methylene C–H bond (pathway A).<sup>14</sup> While this model holds for the majority of the substrates, we believe that the large isopropyl amine substituent in amine **1e** may result in poorer steric differentiation between the two Pd–carboxamide transition states, leading to the formation of both methylene and methyl activated products (Table 1).

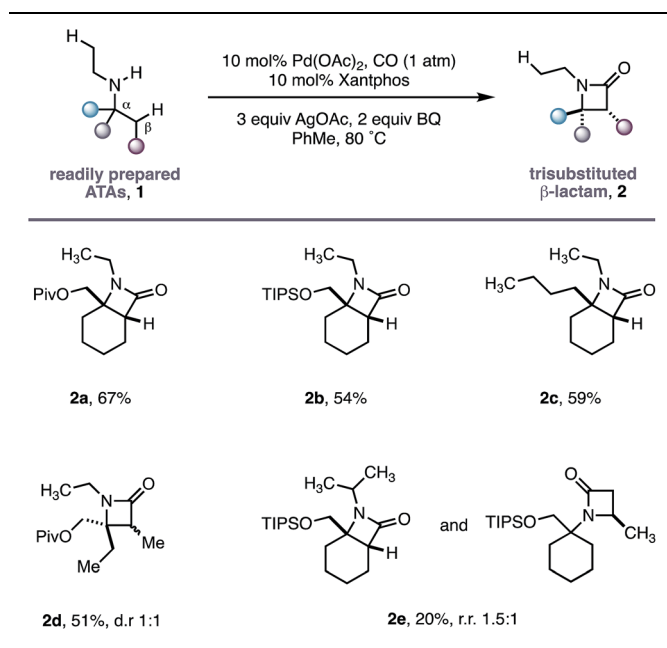
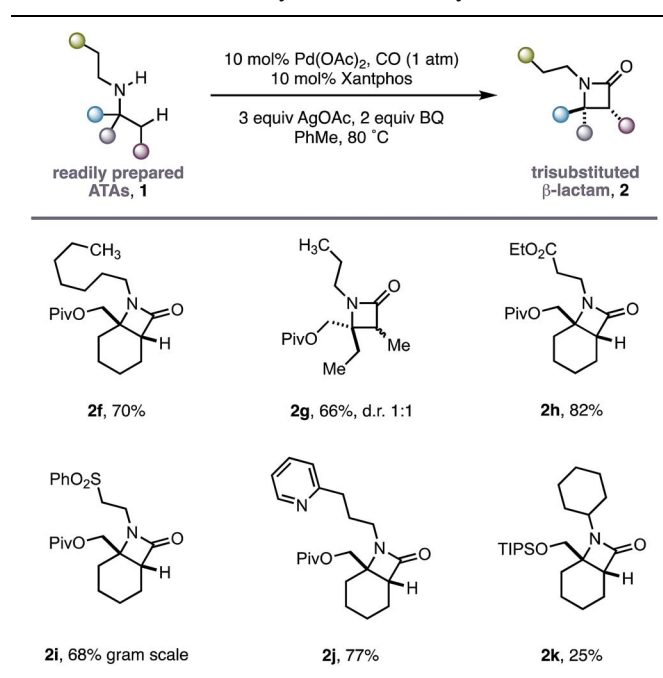
## (a) Selectivity in classical cyclopalladation processes

(b) Previous work – Methyl and methylene  $\beta$ -C–H carbonylation to  $\beta$ -lactams(c) This work – Remarkable selectivity for methylene  $\beta$ -C–H activation

Scheme 1 Overview of C–H carbonylation of aliphatic amines.



Scheme 3 Mechanistic hypothesis for C–H activation of ATAs.

**Table 1** *N*-Ethyl substituted ATA substrate scope for selective methylene C–H carbonylation**Table 2** ATA directed methylene C–H carbonylation

Having successfully demonstrated that a fully substituted centre in the  $\alpha$ -position to the amine is sufficient to induce exclusive  $\beta$ -methylene C–H activation, we next explored how substituents on the non-reacting side of the amine affected the carbonylation process (Table 2). The competing classical 5-membered cyclopalladation was not observed in *n*-propyl-containing amine **2g** or *n*-heptyl amine **2f**, affording the corresponding bicyclic  $\beta$ -lactams in a 66% and 70% yield respectively.  $\beta$ -Amino ester **2h** and sulfone **2i** derivatives bearing acidic  $\alpha$ -hydrogens, which have previously been shown to promote C–H activation,<sup>9</sup> were tolerated in good yield and on gram scale.

The use of Lewis basic heteroaromatics, such as pyridyl motifs, to direct C(sp<sup>3</sup>)-H activation is well established.<sup>5c,15</sup> An amine displaying 2-pyridyl substituent **1j** was tolerated in good yield, with no competitive C–H activation on the propyl chain. Impressively, bis-cyclohexyl substrate **1k**, bearing two very similar sets of methylene C–H bonds, afforded a single  $\beta$ -lactam **2k** with activation occurring exclusively in the  $\alpha$ -position to the quaternary carbon centre.

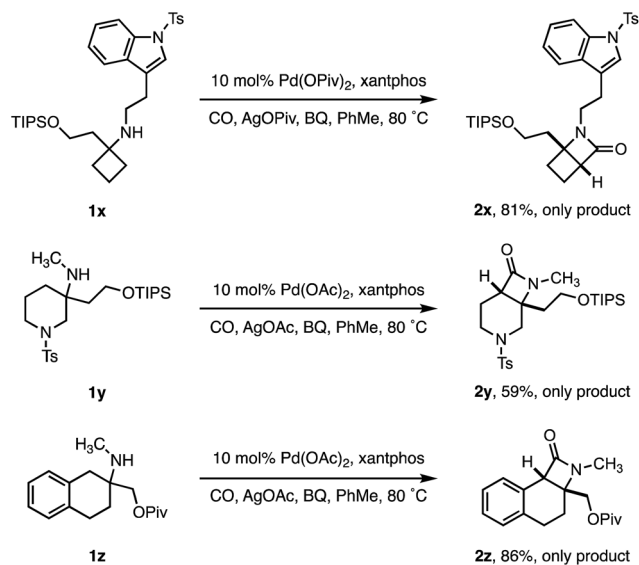
Having established the robustness of this methodology towards a range of functional groups, we turned our attention to substrates containing *N*-methyl amines (Table 3). Despite the ubiquity of *N*-Me amines in biologically active molecules and pharmaceutical agents, their deleterious reactivity with many electrophilic transition metal catalysts has rendered them challenging substrates for C–H activation.<sup>16</sup> The facile oxidation of *N*-methylamines to the corresponding imine followed by nucleophilic capture has been exploited in numerous transformations.<sup>17</sup> Due to the high pharmaceutical utility of *N*-methylamines,<sup>18</sup> we sought to test the limits of our C–H activation methodology by investigating this important class of amine substrate. By virtue of our geometrically locked Pd–

carboxamide intermediate, we reasoned that the *N*-methyl group would be placed in a remote position relative to the reactive palladium centre, thereby enabling a selective process.

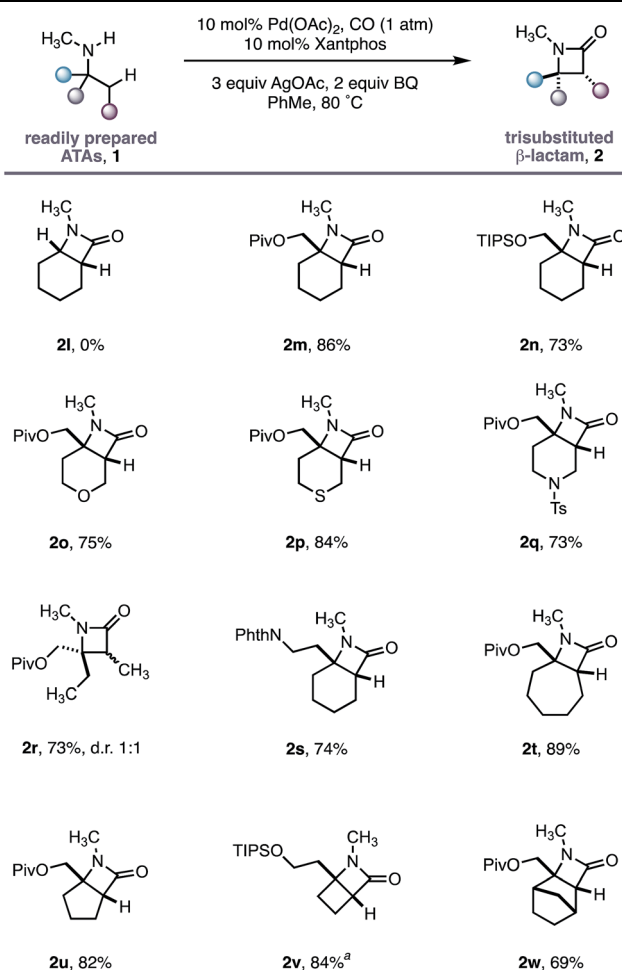
As a control experiment, *N*-methylcyclohexylamine **1l**, lacking the important fully substituted  $\alpha$ -tertiary centre, was subjected to our optimized conditions; none of the desired  $\beta$ -lactam product was observed and the starting amine decomposed. In line with our hypothesis,  $\alpha$ -tertiary amino-alcohol derivatives **1m** and **1n** delivered the corresponding  $\beta$ -lactams (**2m–n**) in good yield without any demethylation. Piperidine and tetrahydropyran motifs are common among pharmaceutical agents but their functionalization at C3 and C4 positions can present a significant challenge;<sup>19</sup> our methodology delivered the bicyclic  $\beta$ -lactam products **2o** and **2q** in good yields, allowing for further derivatization of the C3 position. The reaction also proved to be tolerant of a thioether moiety, known to deactivate transition metal catalysts, delivering the  $\beta$  lactam **2p** in a good 84% yield. Moreover, the reaction proved extremely versatile across a range of ring sizes (**2t** to **2w**) in good yield. Pleasingly, cyclobutylamine **1v** was readily transformed into highly strained 4,4-fused  $\beta$ -lactam **2v**, permitting access to functionalized hydrogenated variants of the ‘Dewar-pyridone’ scaffold.<sup>20</sup>

To test the limits of the positional selectivity of the ATA carbonylation among many potentially reactive C–H bonds, we prepared a range of functional amines that could lead to a number of different lactam products (Scheme 4). Indole rings are considered a ‘privileged’ scaffold in medicinal chemistry,<sup>21</sup> however, they often undergo facile C(sp<sup>2</sup>)-H activation.<sup>22</sup> We were pleased to observe that tryptamine analogue **1x** bearing a cyclobutane ring was readily transformed into the 4,4-fused  $\beta$ -lactam **2x** in good yield without any competing C(sp<sup>2</sup>)-H activation. 3-Methylamino piperidine **1y**, containing two different ring C–H bond environments, afforded complete





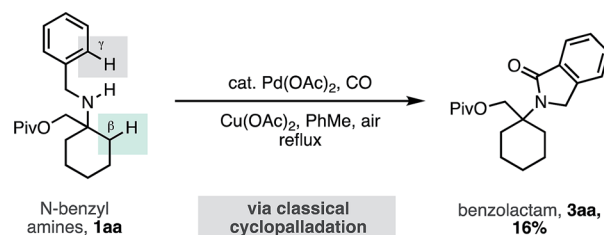
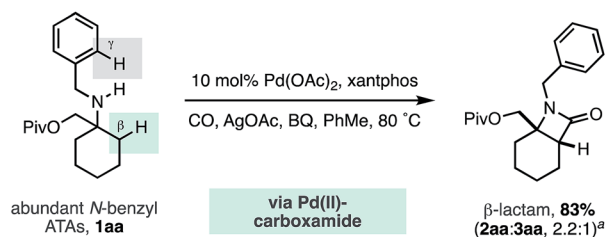
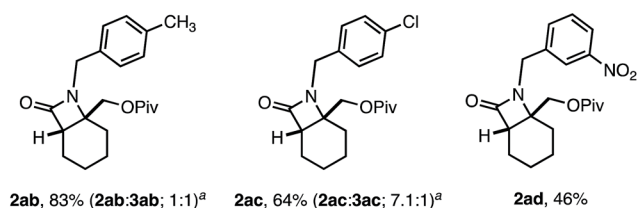
Scheme 4 Selectivity of ATA methylene C–H carbonylation.

Table 3 *N*-Methyl substituted ATAs as substrates for selective methylene C–H carbonylation<sup>a</sup> Reaction with 10 mol% Pd(OPiv)<sub>2</sub> and 3 equiv. AgOPiv.

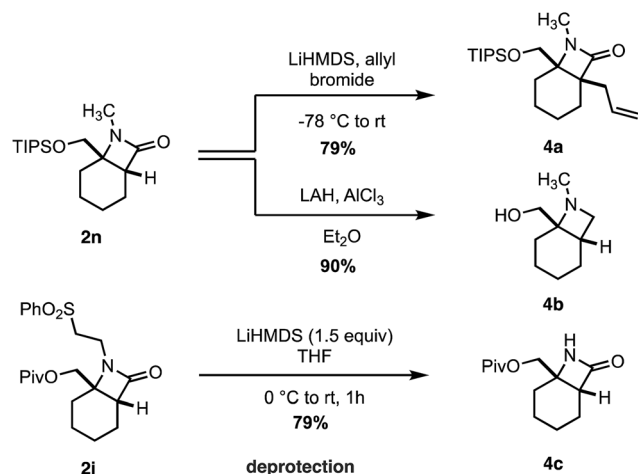
selectivity for the C4 position in useful yield (2y). Similarly, the 2-aminotetralin substrate 1z proved to activate selectively at the benzylic position in good yield, revealing a class of tricyclic  $\beta$ -lactam scaffolds (2z).

To challenge the capacity of the selective C–H carbonylation process, we next designed a substrate that would place a  $\beta$ -methylene C–H bond in competition with a C(sp<sup>2</sup>)–H bond on the ortho position of a benzylamine motif. The cyclopalladation of benzylamines is, arguably, one of the most facile and well understood C–H activation processes, with near exclusive C(sp<sup>2</sup>)–H activation control.<sup>23</sup> Orito and coworkers have shown that alkyl-benzyl substituted secondary amines undergo selective C(sp<sup>2</sup>)–H carbonylation to benzolactams, with no trace of reaction at the C(sp<sup>3</sup>)–H bond (Scheme 5a).<sup>24</sup> To benchmark the reactivity of our alkyl-benzyl amines, we applied Orito's conditions to *N*-benzyl amine derivative 1aa and found that benzolactam 3aa resulting from C(sp<sup>2</sup>)–H activation was produced as the sole product (Scheme 5a).

Upon switching to our optimized C–H carbonylation conditions, we were delighted to see that a mixture of  $\beta$ -lactam 2aa and benzolactam 3aa was formed in a good 83% yield with a 2.2 : 1 ratio in favor of the C(sp<sup>3</sup>)–H activation product 2aa (Scheme 5b). Encouragingly, we found that changing the electronic properties of the aromatic ring had a significant impact

(a) Benzylamine C(sp<sup>2</sup>)–H carbonylation - Orito's conditions(b) Benzylamine C(sp<sup>3</sup>)–H carbonylation via Pd(II) carboxamide(c) Initial scope of benzylamine C(sp<sup>3</sup>)–H carbonylationScheme 5 *N*-Benzyl ATA substrate scope for selective methylene C–H carbonylation. <sup>a</sup>Ratio of  $\beta$ -lactam 2 to  $\gamma$ -benzolactam 3.



Scheme 6 Transformation of  $\beta$ -lactam products.

on the product distribution (Scheme 5c). Electron withdrawing substituents favored  $C(sp^3)$ -H activation, with *m*-NO<sub>2</sub>Ph affording exclusively the  $\beta$ -lactam product **2ad**, with no C-H activation observed on the aromatic ring. These results suggest that classical  $C(sp^2)$ -H activation to the benzolactam occurs *via* an electrophilic cyclopalladation pathway. To the best of our knowledge, this is the first example of a palladium catalyzed C-H activation that is selective for a  $\beta$ -methylene C-H bond in the presence of a  $\gamma$ - $C(sp^2)$ -H bond on an aromatic ring.

Finally, we transformed the  $\beta$ -lactam products into a range of useful chemical building blocks (Scheme 6). Alkylation to form  $\beta$ -lactams displaying vicinal fully substituted stereocenters proceeded in good yield (**4a**). Reduction of **2n** to the corresponding azetidiny alcohol **4b**, a useful class of scaffold in the design of pharmaceutical agents, occurred in an excellent 90% yield. Importantly, the free (NH)lactam **4c** could be obtained in good yield under mild conditions from the corresponding sulfonyl  $\beta$ -lactam **2h**, offering a simple lactam deprotection protocol.

In conclusion, we have developed a remarkable aliphatic amine C-H carbonylation reaction that is capable of selectively activating  $\beta$ -methylene C-H bonds in the presence of traditionally more reactive  $C(sp^3)$  and  $C(sp^2)$ -H bonds. The presence of a fully substituted carbon atom in the  $\alpha$ -position to the amine appears to control this unprecedented selectivity. Using this methodology, a range of highly functionalized  $\beta$ -lactam building blocks have been synthesized in good yields, which can further be derivatised in order to access novel heterocyclic scaffolds that we believe we be useful to a range of synthetic and medicinal applications. Computational studies to explore the origin of this unique selectivity in further detail are currently ongoing within our group.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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## References

- (a) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960; (b) L. McMurray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885; (c) J. Wencel-Delord and F. Glorius, *Nat. Chem.*, 2013, **5**, 369; (d) D. Y.-K. Chen and S. W. Youn, *Chem. -Eur. J.*, 2012, **18**, 9452.
- (a) A. E. Shilov and G. B. Shul'pin, *Chem. Rev.*, 1997, **97**, 2879; (b) K. Godula and D. Sames, *Science*, 2006, **312**, 67; (c) J. A. Labinger and J. E. Bercaw, *Nature*, 2002, **417**, 507.
- J. F. Hartwig, *Acc. Chem. Res.*, 2017, **50**, 549.
- T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147.
- For examples of C-H activation using auxiliaries see: oximes: (a) L. V. Desai, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 9542; oxazolines: (b) R. Giri, X. Chen and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2005, **44**, 2112; picolinamides: (c) V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154; methyl hydroxamic acids: (d) D.-H. Wang, M. Wasa, R. Giri and J.-Q. Yu, *J. Am. Chem. Soc.*, 2008, **130**, 7190; *N*-aryl carboxamides: (e) M. Wasa, K. M. Engle and J.-Q. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 9886; hydroxyl derivatives: (f) Z. Ren, F. Mo and G. Dong, *J. Am. Chem. Soc.*, 2012, **134**, 16991; sulfonamides: (g) K. S. L. Chan, M. Wasa, L. Chu, B. N. Laforteza, M. Miura and J.-Q. Yu, *Nat. Chem.*, 2014, **6**, 146.
- C-H activation using native functionality: pyridines: (a) K. J. Stowers, K. C. Fortner and M. S. Sanford, *J. Am. Chem. Soc.*, 2011, **133**, 6541; alcohols: (b) E. M. Simmons and J. F. Hartwig, *Nature*, 2012, **483**, 70; carboxylic acids: (c) G. Chen, Z. Zhuang, G.-C. Li, T. G. Saint-Denis, Y. Hsiao, C. L. Joe and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2017, **56**, 1506; amines: (d) A. McNally, B. Haffemayer, B. S. L. Collins and M. J. Gaunt, *Nature*, 2014, **510**, 129; (e) J. Calleja, D. Pla, T. W. Gorman, V. Domingo, B. Haffemayer and M. J. Gaunt, *Nat. Chem.*, 2015, **7**, 1009; primary amines using transient directing groups: (f) X. Yu, M. C. Young, C. Wang, D. W. Magness and G. Dong, *Angew. Chem., Int. Ed.*, 2016, **55**, 9084; (g) Y. Wu, Y.-Q. Chen, T. Liu, M. D. Eastgate and J.-Q. Yu, *J. Am. Chem. Soc.*, 2016, **138**, 14554; (h) Y. Liu and H. Ge, *Nat. Chem.*, 2017, **9**, 26.
- D. Willcox, B. G. N. Chappell, K. F. Hogg, J. Calleja, A. P. Smalley and M. J. Gaunt, *Science*, 2016, **354**, 851.
- (a) Z. Huang, C. Wang and G. Dong, *Angew. Chem., Int. Ed.*, 2016, **55**, 5299; (b) N. Gulia and O. Daugulis, *Angew. Chem.*,



- Int. Ed.*, 2017, **56**, 3630; (c) D. Dailier, R. Rocaboy and O. Baudoin, *Angew. Chem., Int. Ed.*, 2017, **56**, 7218.
- 9 J. R. Cabrera-Pardo, A. Trowbridge, M. Nappi, K. Ozaki and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2017, **56**, 11958.
- 10 (a) O. Baudoin, *Acc. Chem. Res.*, 2017, **50**, 1114; for an example of ligand controlled selective methylene C–H activation, see: (b) D. Katayev, M. Nakanishi, T. Bürgi and E. P. Kündig, *Chem. Sci.*, 2012, **3**, 1422.
- 11 A. Hager, N. Vrielink, D. Hager, J. Lefranc and D. Trauner, *Nat. Prod. Rep.*, 2016, **33**, 491.
- 12 We hypothesize that the role of xantphos (or its mono-oxide) is most likely to stabilize the Pd0 species formed at the end of the catalytic cycle prior to its oxidation to the active PdII species required for the reaction. The reaction also works in the absence of xantphos, but the yield of the reaction is significantly lower; see ref. 9.
- 13 Upon subjection of amine **1a** to lower catalyst and ligand loadings of 5 mol% the resulting lactam **2a** was obtained in 43% yield, as determined by <sup>1</sup>H NMR assay.
- 14 We cannot rule out the possibility of classical angle compression (Thorpe-Ingold effect) influencing the selectivity of the C–H activation.
- 15 Selected examples of pyridine-directed C–H activation: (a) A. R. Dick, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 2300; (b) X. Zhao, E. Dimitrijević and V. M. Dong, *J. Am. Chem. Soc.*, 2009, **131**, 3466; (c) X. Chen, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 12634; (d) Y. Zhang, J. Feng and C.-J. Li, *J. Am. Chem. Soc.*, 2008, **130**, 2900; (e) W.-Y. Yu, W. N. Sit, K.-M. Lai, Z. Zhou and A. S. C. Chan, *J. Am. Chem. Soc.*, 2008, **130**, 3304.
- 16 (a) S. Rosseaux, S. I. Gorelsky, B. K. W. Chung and K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 10692; (b) D.-H. Wang, X.-S. Hao, D.-F. Wu and J.-Q. Yu, *Org. Lett.*, 2006, **8**, 3387.
- 17 (a) S. Murahashi, N. Komiya, H. Terai and T. Nakae, *J. Am. Chem. Soc.*, 2003, **125**, 15312; (b) Z. Li and C. J. Li, *J. Am. Chem. Soc.*, 2004, **126**, 11810; (c) Z. Li and C. J. Li, *J. Am. Chem. Soc.*, 2005, **127**, 3672; (d) A. Catino, J. Nichols, B. Nettles and M. Doyle, *J. Am. Chem. Soc.*, 2006, **128**, 5648.
- 18 *Amines: Synthesis, Properties, and Applications*, ed. Lawrence S. A., Cambridge University, Cambridge, 2006.
- 19 C3 functionalisation: (a) D. P. Affron and J. A. Bull, *Eur. J. Org. Chem.*, 2016, 139; (b) J. He, M. Wasa, K. S. L. Chan and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 3387; (c) S. Ye, W. Yang, T. Coon, D. Fanning, T. Neubert, D. Stamos and J.-Q. Yu, *Chem. –Eur. J.*, 2016, **22**, 4748; C4 functionalisation: (d) J. J. Topczewski, P. J. Cabrera, N. I. Saper and M. S. Sanford, *Nature*, 2016, **531**, 220.
- 20 H. Hongo, K. Iwasa, C. Kabuto, H. Matsuzaki and H. Nakano, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1747.
- 21 (a) M.-Z. Zhang, Q. Chen and G.-F. Yang, *Eur. J. Med. Chem.*, 2015, **89**, 421; (b) N. Chadha and O. Silakari, *Eur. J. Med. Chem.*, 2017, **134**, 159.
- 22 (a) E. Beck and M. J. Gaunt, Topic in Current Chemistry, in *C–H activation*, J.-Q. Yu and Z. Shi, Springer-Verlag, Heidelberg, 2010, vol. 292, pp. 87–121; (b) N. Lebrasseur and I. Larrosa, *Adv. Heterocycl. Chem.*, 2012, **105**, 309; (c) N. Lebrasseur and I. Larrosa, *J. Am. Chem. Soc.*, 2008, **130**, 2926; (d) S. Peciado, L. Mendive-Tapia, F. Albericio and R. Lavilla, *J. Org. Chem.*, 2013, **78**, 8129; (e) L. Mendive-Tapia, S. Peciado, J. García, R. Ramón, N. Kielland, F. Albericio and R. Lavilla, *Nat. Commun.*, 2015, **6**, 7160.
- 23 For mechanistic studies, see: (a) A. D. Ryabov, I. K. Sakodinskaya and A. K. Yatsimirsky, *J. Chem. Soc., Dalton Trans.*, 1985, **12**, 2629; (b) D. L. Davies, S. M. A. Donald and S. A. Macgregor, *J. Am. Chem. Soc.*, 2005, **127**, 13754; for stoichiometric examples, see: (c) J. Albert, R. M. Ceder, M. Gomez, J. Granell and J. Sales, *Organometallics*, 1992, **11**, 1536; (d) Y. Fuchita, H. Tsuchiya and A. Miyafuji, *Inorg. Chim. Acta*, 1995, **233**, 91; (e) K. Selvakumar and S. Vancheesan, *Polyhedron*, 1997, **16**, 2405; for catalytic examples, see: (f) A. Lazareva and O. Daugulis, *Org. Lett.*, 2006, **8**, 5211; (g) G. Cai, Y. Fu, Y. Li, X. Wan and Z. Shi, *J. Am. Chem. Soc.*, 2007, **129**, 7666; (h) M. Miura, C.-G. Feng, S. Ma and J.-Q. Yu, *Org. Lett.*, 2013, **15**, 5258; (i) A. Rodríguez, J. Albert, X. Ariza, J. Garcia, J. Granell, J. Farràs, A. La Mela and E. Nicolás, *J. Org. Chem.*, 2014, **79**, 9578; (j) P. W. Tan, M. Haughey and D. J. Dixon, *Chem. Commun.*, 2015, **51**, 4406; (k) H. Li, G.-X. Cai and Z.-J. Shi, *Dalton Trans.*, 2010, **39**, 10442.
- 24 (a) K. Orito, A. Horibata, T. Nakamura, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita and M. Tokuda, *J. Am. Chem. Soc.*, 2004, **126**, 14342; (b) K. Orito, M. Miyazawa, T. Nakamura, A. Horibata, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita, T. Yamazaki and M. Tokuda, *J. Org. Chem.*, 2006, **71**, 5951.



# Multicomponent synthesis of tertiary alkylamines by photocatalytic olefin–hydroaminoalkylation

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There is evidence to suggest that increasing the level of saturation (that is, the number of  $sp^3$ -hybridized carbon atoms) of small molecules can increase their likelihood of success in the drug discovery pipeline<sup>1</sup>. Owing to their favourable physical properties, alkylamines have become ubiquitous among pharmaceutical agents, small-molecule biological probes and pre-clinical candidates<sup>2</sup>. Despite their importance, the synthesis of amines is still dominated by two methods: *N*-alkylation and carbonyl reductive amination<sup>3</sup>. Therefore, the increasing demand for saturated polar molecules in drug discovery has continued to drive the development of practical catalytic methods for the synthesis of complex alkylamines<sup>4–7</sup>. In particular, processes that transform accessible feedstocks into  $sp^3$ -rich architectures provide a strategic advantage in the synthesis of complex alkylamines. Here we report a multicomponent, reductive photocatalytic technology that combines readily available dialkylamines, carbonyls and alkenes to build architecturally complex and functionally diverse tertiary alkylamines in a single step. This olefin–hydroaminoalkylation process involves a visible-light-mediated reduction of in-situ-generated iminium ions to selectively furnish previously inaccessible alkyl-substituted  $\alpha$ -amino radicals, which subsequently react with alkenes to form  $C(sp^3)$ – $C(sp^3)$  bonds. The operationally straightforward reaction exhibits broad functional-group tolerance, facilitates the synthesis of drug-like amines that are not readily accessible by other methods and is amenable to late-stage functionalization applications, making it of interest in areas such as pharmaceutical and agrochemical research.

The physiological properties of tertiary aliphatic amines and their ability to interfere with natural neurotransmission pathways have rendered them highly effective pharmaceutical agents<sup>8</sup>, in areas that range from the treatment of neurodegenerative disorders (such as Alzheimer's disease)<sup>9</sup> to metabolic syndromes (such as obesity)<sup>10</sup> (Fig. 1a). Traditionally, synthetic routes towards these molecules have required multiple steps and tedious purifications, which severely hamper drug discovery efforts. Therefore, the development of straightforward methods that enable the construction of complex tertiary amines from simple starting materials would have far-reaching implications for both the synthetic and the medicinal chemistry communities. Whereas the abundance, diversity and predictable reactivity of  $sp^2$ -hybridized feedstocks has led to the emergence of new transition-metal-catalysed methods of amine synthesis—namely the Buchwald–Hartwig amination<sup>11</sup> and olefin–hydroamination<sup>12–14</sup>—strategies for the synthesis of more complex alkylamines are more limited<sup>13–15</sup>. We reasoned that an operationally simple and mechanistically distinct catalytic process involving available dialkylamines, olefins and aliphatic carbonyl feedstocks would expand the capacity of olefin–hydroaminoalkylation-based strategies to the synthesis of tertiary alkylamines.

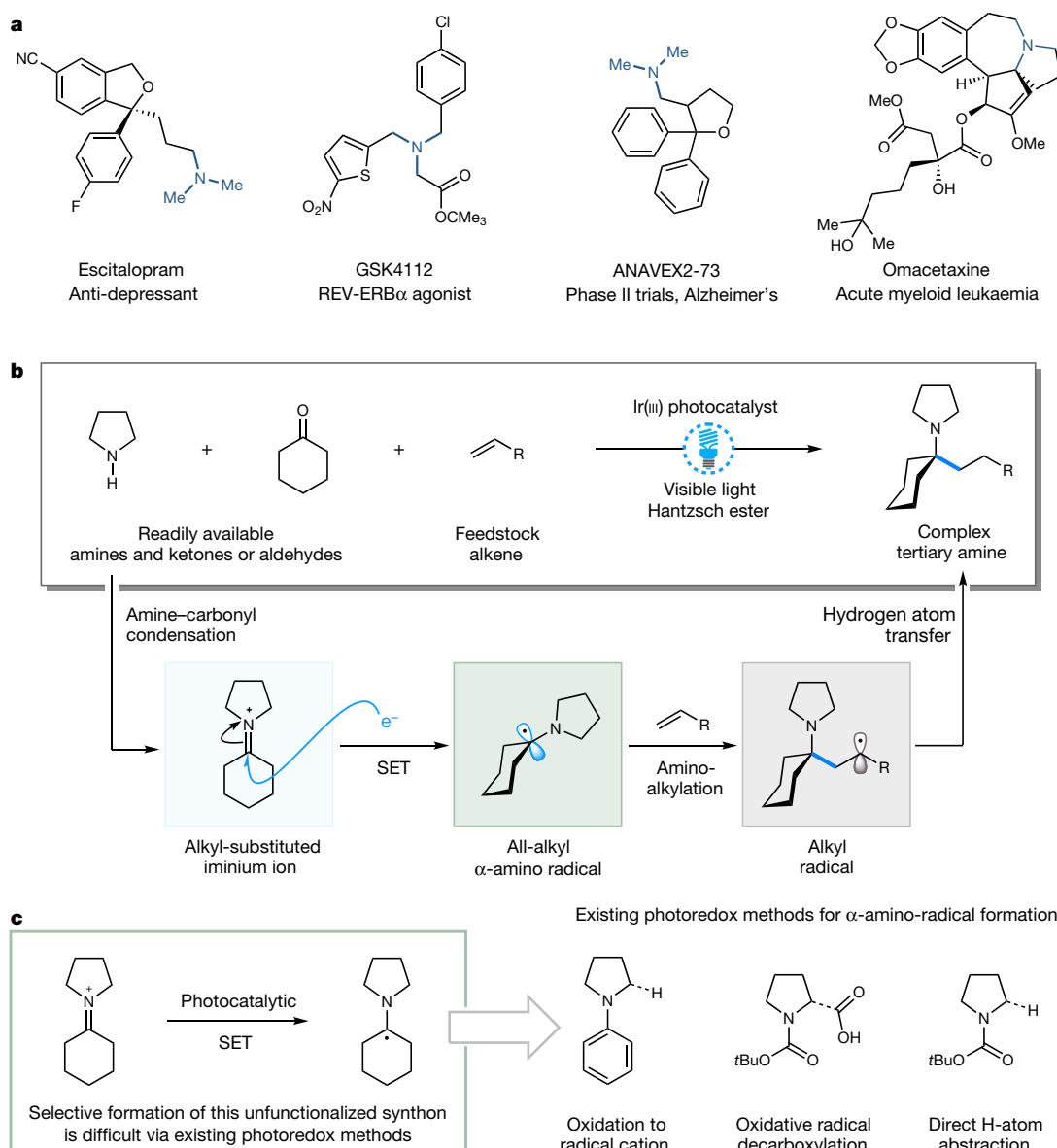
We proposed that an electrophilic iminium ion, formed through the well established reaction between secondary alkylamines and alkyl-substituted carbonyls, could be susceptible to a catalytic single-electron reduction process (Fig. 1b). The resulting  $\alpha$ -amino radical could then engage a third reaction component, such as an alkene, in a subsequent

cross-coupling reaction to form a  $C(sp^3)$ – $C(sp^3)$  bond. However, there are few methods that report the generation of 'all-alkyl'  $\alpha$ -amino radicals from pre-formed iminium ions, and all have issues relating to their practical application. Subsequently, addition of such  $\alpha$ -amino radicals to alkenes has been limited to specific intramolecular examples<sup>16,17</sup>. To overcome these problems we proposed that, first, a visible-light-activated photocatalyst could mediate single-electron transfer (SET) to an in-situ-generated alkyl-substituted iminium ion, generating the desired  $\alpha$ -amino radical under mild reaction conditions (Fig. 1b). Second, we considered that a polarity-matched hydrogen-atom transfer (HAT) from a suitable reagent could facilitate cross-coupling to the alkene by intercepting the resulting alkyl-substituted radical. An important feature of this proposed catalytic activation pathway is the regiospecific positioning of the newly formed  $\alpha$ -amino radical, made possible by the SET to the iminium ion, regardless of the groups surrounding the reactive centre. Selective formation of an 'all-alkyl'  $\alpha$ -amino radical would not be possible via related photocatalytic approaches without the use of pre-functionalized starting materials or inherently selective substrates<sup>18–20</sup> (Fig. 1c).

We were mindful of several factors that could impede the development of the photocatalytic olefin–hydroaminoalkylation process. Whereas protonated imines and iminium ions that are conjugated with multiple aromatic substituents (half-wave reduction potential,  $E_{1/2}^{\text{red}} = -0.8$  to  $-1.2$  V versus saturated calomel electrode (SCE) in acetonitrile)<sup>21</sup> have been found to partake in a limited range of reductive coupling reactions<sup>22,23</sup>, the reduction potential of an 'all-alkyl' iminium ion could be up to  $E_{1/2}^{\text{red}} = -1.95$  V (versus SCE in acetonitrile)<sup>21</sup> and would require a highly reducing photocatalyst that may be incompatible with existing functional groups. Moreover, alkyliminium ions are known to exist in (often unfavourable) equilibrium with the corresponding enamines, which can also undergo SET reactions to form radical species, presenting competing pathways<sup>24</sup>. Finally, the addition of  $\alpha$ -amino radicals to simple alkenes is known to be low-yielding owing to oligomerization of the resulting radical<sup>25</sup>. We hereby report a comprehensive strategy for the modular and efficient construction of complex tertiary alkylamines via photocatalytic olefin–hydroaminoalkylation.

The initial evaluation of the proposed amine synthesis focused on a reaction between butyraldehyde **1a**, dibenzylamine **2a**, butyl acrylate **3a** and Hantzsch ester **4a** catalysed by  $\text{Ir}(\text{ppy})_3$  (ppy, 2-phenylpyridinato), under irradiation by visible light (Fig. 2a). Optimized reaction conditions were readily established (for a detailed account of the optimization study, see Supplementary Materials), using 1 mol%  $\text{Ir}(\text{ppy})_3$  and a 40 W blue light-emitting diode (LED) for 2 hours at room temperature. Under these conditions, near-equimolar quantities of aldehyde, amine and alkene, with 1.5 equivalents of Hantzsch ester in a 0.1 M solution of dichloromethane containing molecular sieves and 20 mol% of propionic acid, formed the desired amine **5a**, which was isolated in 84% yield after chromatography (Fig. 2b). The reaction displayed remarkable selectivity; we observed only trace quantities of the reductive-amination side product, which presumably resulted from HAT to the  $\alpha$ -amino radical from **4a**<sup>26</sup>.

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**Fig. 1 | Evolution of a strategy for the multicomponent photocatalytic synthesis of tertiary alkylamines. a,** Examples highlighting the importance of tertiary amines in the pharmaceutical industry. **b,** Multicomponent photocatalytic olefin-hydroaminoalkylation to yield

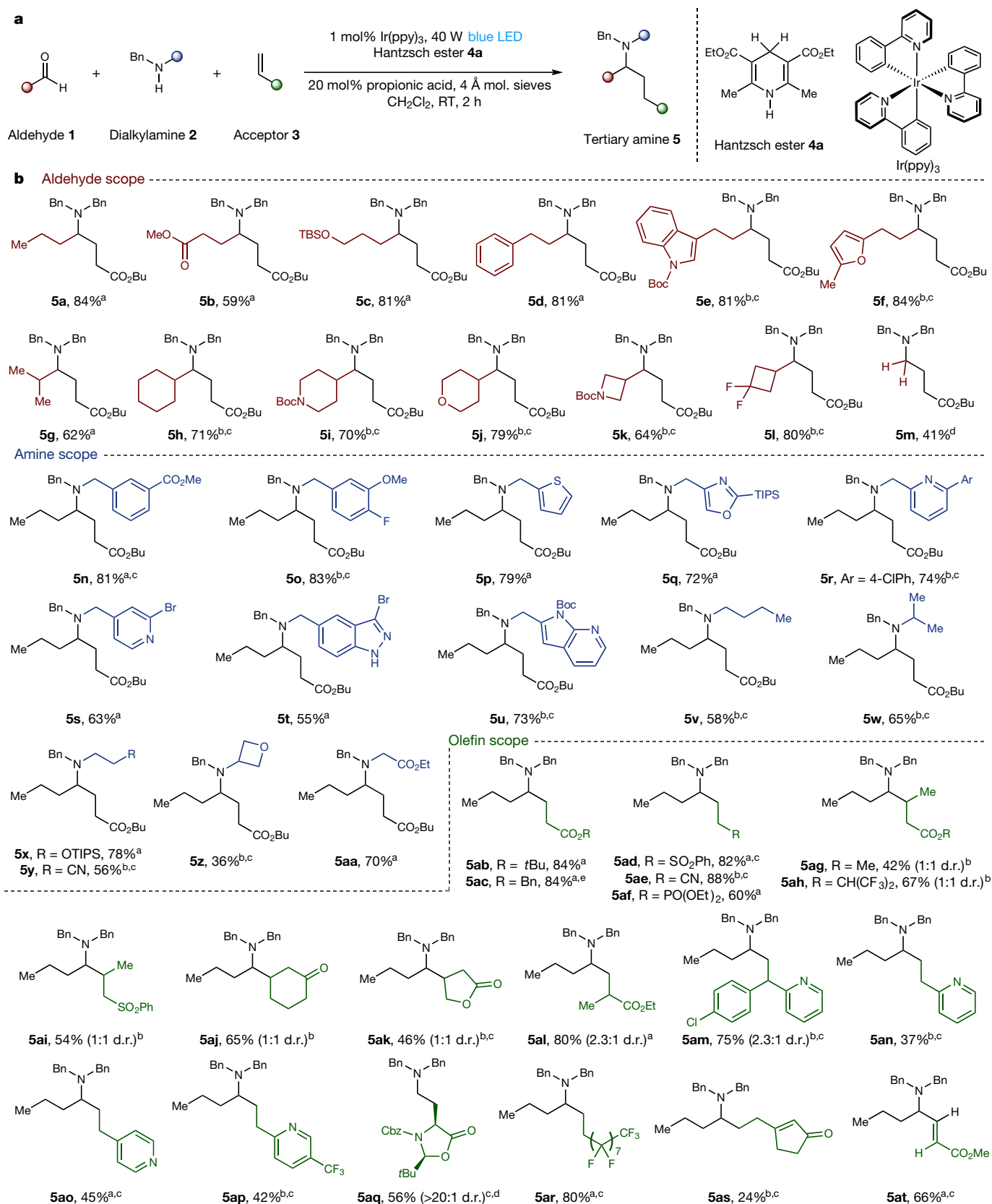
Under the optimized conditions we found that various linear aldehydes, including those bearing electron-rich heteroarenes, reacted efficiently to give amines **5a–5f** in good yields (Fig. 2b). Aldehydes displaying  $\alpha$ -branching produced the expected amines **5g–5l** in good yield; notable examples included saturated heterocycles and strained ring features often found in pharmaceutical agents. The  $\alpha$ -amino radical formed from formaldehyde and dibenzylamine was effective in the reaction, producing the  $\gamma$ -aminobutyric-acid derivative **5m**; however, benzaldehyde-derived iminium ions failed to deliver the desired cross-coupling products. Next, we found that benzylamine derivatives containing many different functionalized aryl and heteroaryl groups were amenable to the reaction and gave good yields of the corresponding amines **5n–5u**. Amines displaying linear and branched alkyl substituents, as well as ester, hydroxyl and nitrile functionality, reacted well to give amines **5v–5aa**. The photocatalytic process was effective with a range of electron-deficient alkenes. A reaction with benzyl acrylate **3c** could be adapted to a gram-scale process, yielding 1.4 g of product **5ac** in 84% yield. Notably, acrylonitrile (giving **5ae**) proved a suitable coupling partner, despite being prone to oligomerization in radical

tertiary alkylamines via the selective formation of alkyl-substituted  $\alpha$ -amino radicals. **c,** Catalytic photoredox methods for the generation of  $\alpha$ -amino radicals.

reactions. Substituents at either the  $\alpha$ - or the  $\beta$ -positions on the alkene (**5ag–5ak**) could be accommodated despite the lower electrophilicity and greater steric demand of these acceptors, with a diastereoselectivity of 2.3:1 observed in the reaction of methacrylate to form **5al**. Vinyl pyridine derivatives also proved to be viable acceptors (giving **5am–5ap**), enabling facile access to chlorphenamine derivative **5am**. The addition of the  $\alpha$ -amino radical to a chiral dehydroalanine derivative led to enantioenriched non-proteogenic amino acid derivative **5aq** in good yield. We also found that perfluorinated alkenes, dienes and electron-deficient alkynes functioned well as acceptors (giving **5ar–5at**); the reaction with methyl propiolate delivered (*E*)-allylic amine **5at** in 66% yield as a single geometric isomer.

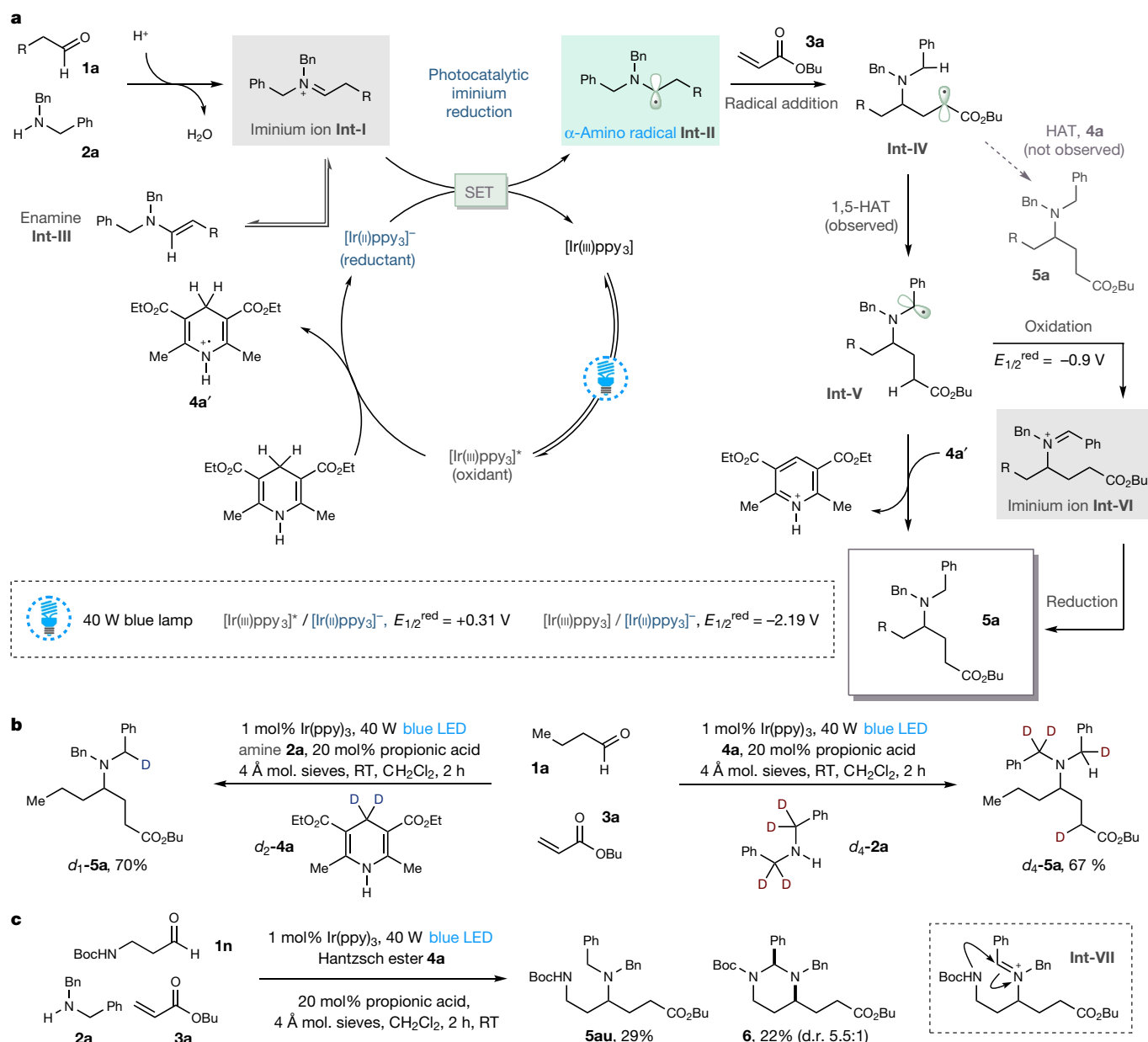
Our mechanistic proposal for the photocatalytic olefin-hydroaminoalkylation is shown in Fig. 3a. The reaction begins with visible-light excitation of Ir(ppy)<sub>3</sub> to the long-lived photoexcited  $^*Ir(III)$  species, with a lifetime<sup>27</sup>,  $\tau$ , of 1.9  $\mu$ s. Although this species may be sufficiently reducing (Ir(IV)/ $^*Ir(III)$ ,  $E_{1/2}^{red} = -1.73$  V versus SCE in acetonitrile)<sup>27</sup> to undergo SET to alkyliminium ion **Int-I**, we recognized that  $^*Ir(III)ppy_3$  is efficiently quenched by Hantzsch ester **4a** ( $^*Ir(III)/Ir(II)$ ,





**Fig. 2 | Scope of the multicomponent photocatalytic synthesis of tertiary alkylamines.** **a**, Optimized conditions for photocatalytic olefin-hydroaminoalkylation. **b**, Scope of photocatalytic olefin-hydroaminoalkylation. <sup>a</sup>amine:aldehyde:acceptor (1:1:1:1), **4a** (1.5 equiv.); <sup>b</sup>amine:aldehyde:acceptor (1:2:2), **4a** (1.5 equiv.); <sup>c</sup>methoxyethyl-

Hantzsch ester (1.5 equiv.); <sup>d</sup>paraformaldehyde (5 equiv.), preheated for 1 h; <sup>e</sup>4 mmol scale. Boc, *tert*-butoxycarbonyl; Cbz, benzyloxycarbonyl; d.r., diastereomeric ratio; ppy, 2-phenylpyridinato; RT, room temperature; TBS, *tert*-butyldimethylsilyl; TIPS, triisopropylsilyl.

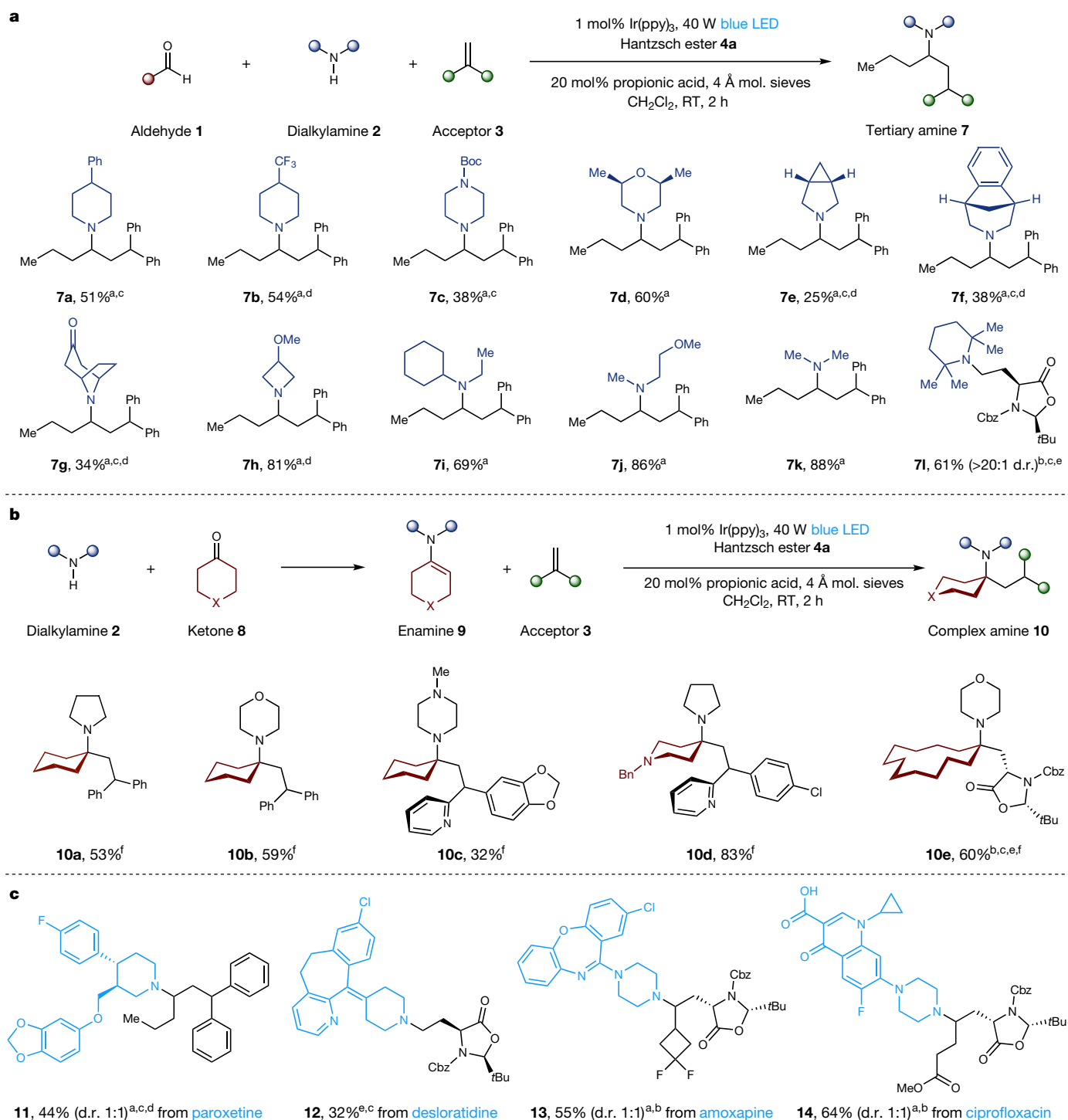


**Fig. 3 | Studies towards understanding the mechanism of the multicomponent photocatalytic synthesis of tertiary alkylamines. a, Proposed mechanism for the photocatalytic olefin-**

**hydroaminoalkylation. R = Et. b, Deuterium-labelling studies. c, Evidence for the iminium-ion redox-relay mechanism.**

$E_{1/2}^{\text{red}} = +0.31$  V versus SCE in acetonitrile<sup>27</sup> leading to  $[\text{Ir}(\text{II})\text{ppy}_3]^-$  and the corresponding Hantzsch ester-radical cation **4a'**. Importantly,  $[\text{Ir}(\text{II})\text{ppy}_3]^-$  is sufficiently reducing ( $\text{Ir}(\text{III})/\text{Ir}(\text{II})$ ,  $E_{1/2}^{\text{red}} = -2.19$  V versus SCE in acetonitrile)<sup>27</sup> to undergo SET with the full range of alkyliminium ions<sup>21</sup>, leading to  $\alpha$ -amino radical **Int-II**. We identified enamine **Int-III** as the predominant species in the  $^1\text{H}$  NMR spectrum of the reaction mixture; we believe this is an off-cycle precursor to the iminium ion **Int-I**, with the acid maintaining a low concentration of iminium **Int-I** by protonation of enamine **Int-III**. The  $\alpha$ -amino radical **Int-II** now engages the polarity-matched acrylate **3a**, creating a carbon–carbon bond and  $\alpha$ -ester radical **Int-IV**. Given the propensity for monosubstituted  $\alpha$ -ester radical **Int-IV** to undergo oligomerization<sup>25</sup>, we anticipated that an intramolecular 1,5-HAT to the benzylic position may act as a kinetic trap to form stabilized radical **Int-V**<sup>28</sup>. Finally, we expected that the Hantzsch ester **4a** or its radical cation **4a'** would participate in a HAT reaction with **Int-V** to form amine **5a**. A reaction using deuterium-labelled Hantzsch ester **d<sub>2</sub>-4a** (Fig. 3b) confirmed our hypothesis; deuterium was incorporated exclusively at

the benzylic position of amine **d<sub>1</sub>-5a**, showing that 1,5-HAT occurred before interception with **4a** or **4a'**. This theory was further corroborated using labelled dibenzylamine **d<sub>4</sub>-2a**, wherein a deuterium atom was transferred to the position adjacent to the ester in amine **d<sub>4</sub>-5a**. We also found that an aldehyde bearing a  $\beta$ -nucleophilic group (**1n**) underwent cyclization onto the benzylic position to form **6**, as a side reaction in the formation of **5au** (Fig. 3c). This result suggests that the  $\alpha$ -aminobenzyl radical (**Int-V**) can undergo oxidation ( $E_{1/2}^{\text{red}} = -0.9$  V versus SCE in acetonitrile)<sup>29</sup> to iminium **Int-VI**, which is accessible to a range of oxidants including  $^*\text{Ir}(\text{III})$ <sup>27</sup>. The selective reduction of benzaldiminium ion **Int-VI** over the initially formed iminium **Int-I** can be rationalized by the inability of **Int-VI** to form a stable enamine intermediate, compared to the interconversion between **Int-I** and **Int-III**. The reduction of **Int-VI** can proceed either by a two-electron process with **4a** or by photocatalytic SET and HAT. Notably, a pathway whereby iminium **Int-I** is translated into a new iminium species **Int-VI** represents an overall mechanism that can be described as a redox relay of iminium ions, which, to the best of our knowledge, has not been reported previously.



**Fig. 4 | Expanding the scope of the multicomponent photocatalytic synthesis of tertiary alkylamines. a**, Scope of non-benzylic amines in the photocatalytic olefin-hydroaminoalkylation. **b**, The synthesis of alkyl-substituted  $\alpha$ -tertiary amines from dialkylketones. **c**, Late-stage photocatalytic olefin-hydroaminoalkylation with pharmaceutical agents.

In this context, benzylamines not only overcome the inherent challenges posed by the addition of  $\alpha$ -amino radicals to electron-deficient alkenes, but also act as a protecting group for primary and secondary alkylamines. Nonetheless, we reasoned that the use of an alkene that would produce a less-electrophilic radical should favour direct reaction with the Hantzsch ester-radical cation **4a'**, obviating the need for the 1,5-HAT process, and hence permitting the use of various dialkylamines. To test this, 1,1-diphenylethylene was combined with aldehyde **1a** and 4-phenylpiperidine under the standard conditions, upon which

the desired tertiary amine **7a** was formed in 51% yield (Fig. 4a). Other amine heterocycles were also compatible with this alkene acceptor, giving the amine products **7b–7k** in good yield; notably, 1,1-diarylpropylamines are key motifs commonly found in H<sub>1</sub>-antihistamines<sup>30</sup>. Among these examples, a number of amines found in pharmaceuticals formed the corresponding complex tertiary amines (**7c–7h**), demonstrating the potential to construct 'drug-like' molecules in a single step from readily available materials. The use of non-benzylic amines was not restricted to reactions with 1,1-diarylethenes; the reaction of

<sup>a</sup>amine:aldehyde:acceptor (1:2:2), **4a** (1.5 equiv.); <sup>b</sup>acceptor (1.5 equiv.); <sup>c</sup>methoxyethyl-Hantzsch ester (1.5 equiv.); <sup>d</sup>amine hydrochloride and Et<sub>3</sub>N (1 equiv.); <sup>e</sup>paraformaldehyde (5 equiv.), preheated for 1 h; <sup>f</sup>enamine (1 equiv.), acceptor (2 equiv.).

tetramethylpiperidine, formaldehyde and a dehydroalanine acceptor proceeded smoothly to form amine **71** as a single diastereomer.

We anticipated that the use of dialkylketones would be an important extension to the photocatalytic process, because these reactions would give rise to  $\alpha$ -tertiary amine products<sup>31</sup>. Aware that the formation of ketiminium ions often requires more forcing conditions, we reasoned that protonation of a pre-formed enamine **9** would provide a more accessible source of alkylketiminium ions, as alkyl enamines can be readily prepared on a gram scale in one step (Fig. 4b). Under the standard conditions, a range of alkyl enamines underwent smooth cross-coupling with alkene acceptors to form  $\alpha$ -tertiary amines **10a–10e**. The olefin–hydroaminoalkylation method was able to generate complex  $\alpha$ -tertiary alkylamine scaffolds in a single step; such scaffolds would be difficult to assemble using classical methods.

Given that dialkylamine motifs are present in a range of small-molecule drugs and pre-clinical candidates, the late-stage functionalization of such molecules would be a powerful demonstration of the utility of this process. To confirm this strategy, we selected four pharmaceutical agents and subjected them to the photocatalytic reaction (Fig. 4c). Each of these architecturally complex amines underwent smooth olefin–hydroaminoalkylation with a variety of aldehydes to furnish the tertiary amine products **11–14**. In particular, the combination of desloratidine with formaldehyde and a chiral dehydroalanine acceptor forms a single diastereomer of the tertiary amine derivative **12**, constituting a potentially useful linker strategy through which further functionalization of drug scaffolds could be realized.

We expect that the operational simplicity, efficacy and broad scope of this highly selective, multicomponent photocatalytic amine synthesis will find widespread use among organic chemistry end-users both in academia and in industry. Moreover, we believe that the convenience with which this method generates underexplored alkyl-substituted  $\alpha$ -amino radicals will inspire further advances in the synthesis of complex tertiary amine scaffolds.

## Data availability

The data that support the findings of this study are available within the paper and its supplementary information files. Raw data are available from the corresponding author on reasonable request. Materials and methods, experimental procedures, useful information, mechanistic studies, optimization studies, <sup>1</sup>H NMR spectra, <sup>13</sup>C NMR spectra and mass spectrometry data are available in the Supplementary Materials. Crystallographic data are available free of charge from the Cambridge Crystallographic Data Centre (<https://www.ccdc.cam.ac.uk/>) under reference number CCDC 1819790.

## Online content

Any methods, additional references, Nature Research reporting summaries, source data, statements of data availability and associated accession codes are available at <https://doi.org/10.1038/s41586-018-0537-9>.

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- Lovering, F., Bikker, J. & Humblet, C. Escape from flatland: Increasing saturation as an approach to improving clinical success. *J. Med. Chem.* **52**, 6752–6756 (2009).
- Blakemore, D. C. et al. Organic synthesis provides opportunities to transform drug discovery. *Nat. Chem.* **10**, 383–394 (2018).
- Roughley, S. D. & Jordan, A. M. The medicinal chemist's toolbox: An analysis of reactions used in the pursuit of drug candidates. *J. Med. Chem.* **54**, 3451–3479 (2011).
- Yang, Y., Shi, S.-L., Niu, D., Liu, P. & Buchwald, S. L. Catalytic asymmetric hydroamination of unactivated internal olefins to aliphatic amines. *Science* **349**, 62–66 (2015).
- Musacchio, A. J. et al. Catalytic intermolecular hydroaminations of unactivated olefins with secondary alkyl amines. *Science* **355**, 727–730 (2017).
- Johnston, C. P., Smith, R. T., Allmendinger, S. & MacMillan, D. W. C. Metallophotoredox-catalysed  $sp^3$ – $sp^3$  cross-coupling of carboxylic acids with alkyl halides. *Nature* **536**, 322–325 (2016).
- Matier, C. D., Schwaben, J., Peters, J. C. & Fu, G. C. Copper-catalyzed alkylation of aliphatic amines induced by visible light. *J. Am. Chem. Soc.* **139**, 17707–17710 (2017).
- Mayol-Llinàs, J., Nelson, A., Farnaby, W. & Ayscough, A. Assessing molecular scaffolds for CNS drug discovery. *Drug Discov. Today* **22**, 965–969 (2017).
- Lahmy, V., Long, R., Morin, D., Villard, V. & Maurice, T. Mitochondrial protection by the mixed muscarinic/ $\sigma_1$  ligand ANAVEX2–73, a tetrahydrofuran derivative, in A $\beta$ <sub>25–35</sub> peptide-injected mice, a nontransgenic Alzheimer's disease model. *Front. Cell. Neurosci.* **8**, 463 (2015).
- Marciano, D. P. et al. The therapeutic potential of nuclear receptor modulators for treatment of metabolic disorders: PPAR $\gamma$ , RORs, Rev-erbs. *Cell Metab.* **19**, 193–208 (2014).
- Ruiz-Castillo, P. & Buchwald, S. L. Application of palladium-catalyzed C–N cross-coupling reactions. *Chem. Rev.* **116**, 12564–12649 (2016).
- Huang, L., Arndt, M., Gooßen, K., Heydt, H. & Gooßen, L. J. Late transition metal-catalyzed hydroamination and hydroamidation. *Chem. Rev.* **115**, 2596–2697 (2015).
- Kalck, P. & Urrutigoity, M. Tandem hydroaminomethylation reaction to synthesize amines from alkenes. *Chem. Rev.* **118**, 3833–3861 (2018).
- Herzon, S. B. & Hartwig, J. F. Hydroaminoalkylation of unactivated olefins with dialkylamines. *J. Am. Chem. Soc.* **130**, 14940–14941 (2008).
- Perez, F., Oda, S., Geary, L. M. & Krische, M. J. Ruthenium catalyzed transfer hydrogenation for C–C bond formation: hydrohydroxyalkylation and hydroaminoalkylation via reactant redox pairs. *Top. Curr. Chem.* **374**, 35 (2016).
- Renaud, P. & Giraud, L. 1-Amino- and 1-amidoalkyl radicals: generation and stereoselective reactions. *Synthesis* **1996**, 913–926 (1996).
- Mariano, P. S. Electron-transfer mechanisms in photochemical transformations of iminium salts. *Acc. Chem. Res.* **16**, 130–137 (1983).
- Chu, L., Ohta, C., Zuo, Z. & MacMillan, D. W. C. Carboxylic acids as a traceless activation group for conjugate additions: a three-step synthesis of ( $\pm$ )-pregabalin. *J. Am. Chem. Soc.* **136**, 10886–10889 (2014).
- Nakajima, K., Miyake, Y. & Nishibayashi, Y. Synthetic utilization of  $\alpha$ -amino radicals and related species in visible light photoredox catalysis. *Acc. Chem. Res.* **49**, 1946–1956 (2016).
- Thullen, S. M. & Rovis, T. A mild hydroaminoalkylation of conjugated dienes using a unified cobalt and photoredox catalytic system. *J. Am. Chem. Soc.* **139**, 15504–15508 (2017).
- Andrieux, C. P. & Savéant, J. M. Electrodimerization: II. Reduction mechanism of immonium cations. *J. Electroanal. Chem.* **26**, 223–235 (1970).
- Lee, K. N. & Ngai, M.-Y. Recent developments in transition-metal photoredox-catalysed reactions of carbonyl derivatives. *Chem. Commun.* **53**, 13093–13112 (2017).
- Heinz, C. et al. Ni-catalyzed carbon–carbon bond-forming reductive amination. *J. Am. Chem. Soc.* **140**, 2292–2300 (2018).
- Capacci, A. G., Malinowski, J. T., McAlpine, M. J., Kuhne, J. & MacMillan, D. W. C. Direct, enantioselective  $\alpha$ -alkylation of aldehydes using simple olefins. *Nat. Chem.* **9**, 1073–1077 (2017).
- Dai, X. et al. The coupling of tertiary amines and acrylate derivatives via visible-light photoredox catalysis. *J. Org. Chem.* **79**, 7212–7219 (2014).
- Guo, X. & Wenger, O. S. Reductive amination by photoredox catalysis and polarity-matched hydrogen atom transfer. *Angew. Chem. Int. Ed.* **57**, 2469–2473 (2018).
- Flamigni, L., Barbieri, A., Sabatini, C., Ventura, B. & Barigelletti, F. Photochemistry and photophysics of coordination compounds: iridium. *Top. Curr. Chem.* **281**, 143–203 (2007).
- Yu, P. et al. Enantioselective C–H bond functionalization triggered by radical trifluoromethylation of unactivated alkene. *Angew. Chem. Int. Ed.* **53**, 11890–11894 (2014).
- Wayner, D. D. M., Dannenberg, J. J. & Griller, D. Oxidation potentials of  $\alpha$ -aminoalkyl radicals: bond dissociation energies for related radical cations. *Chem. Phys. Lett.* **131**, 189–191 (1986).
- Simons, F. E. R. Advances in H<sub>1</sub>-antihistamines. *N. Engl. J. Med.* **351**, 2203–2217 (2004).
- Hager, A., Vrielink, N., Hager, D., Lefranc, J. & Trauner, D. Synthetic approaches towards alkaloids bearing  $\alpha$ -tertiary amines. *Nat. Prod. Rep.* **33**, 491–522 (2016).

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**Author contributions** M.J.G., A.T. and D.R. designed the experiments. A.T. and D.R. performed and analysed the experiments. M.J.G., A.T. and D.R. prepared the manuscript.

**Competing interests** The authors declare no competing interests.

## Additional information

**Supplementary information** is available for this paper at <https://doi.org/10.1038/s41586-018-0537-9>.

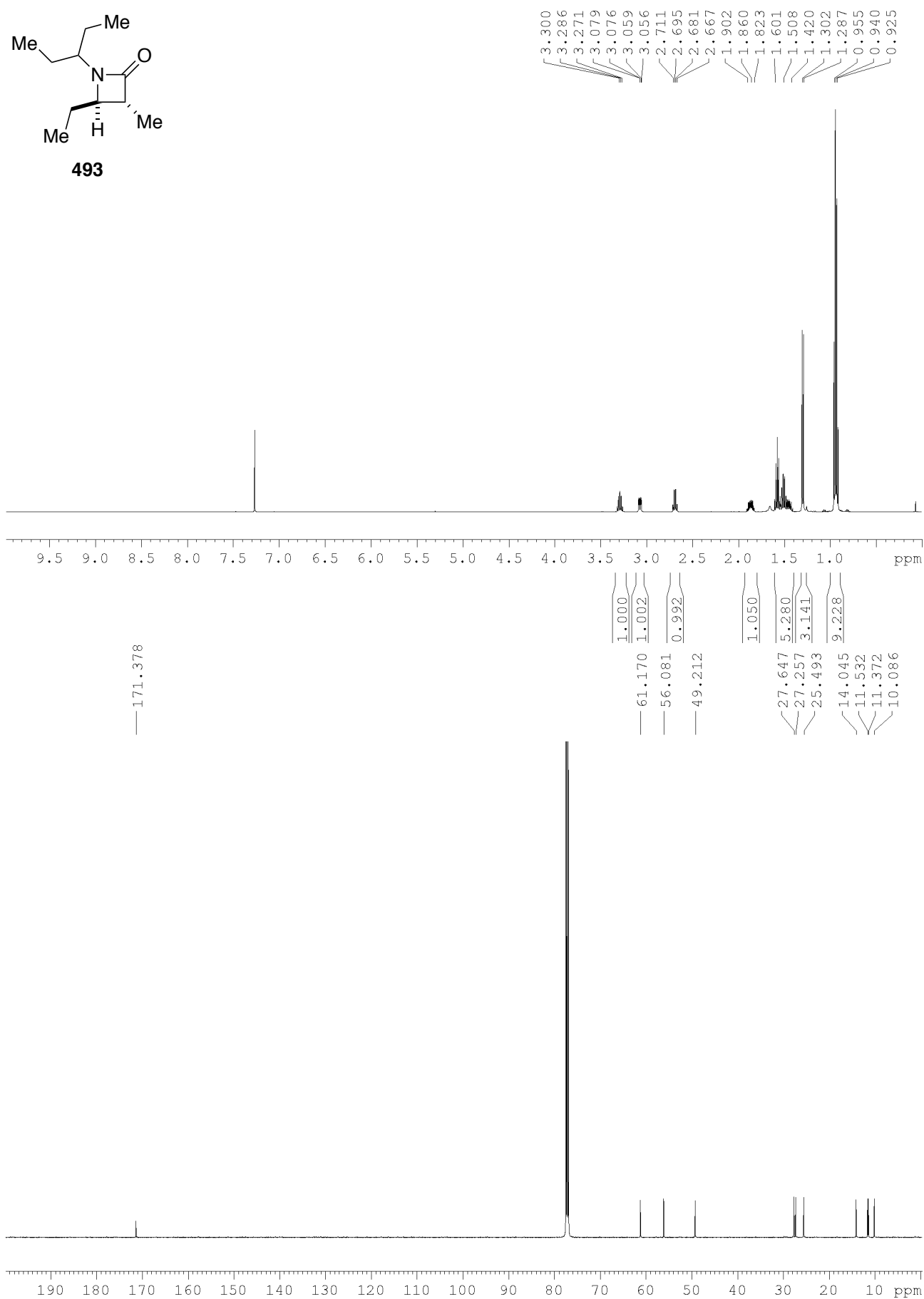
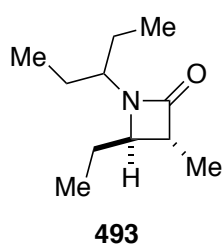
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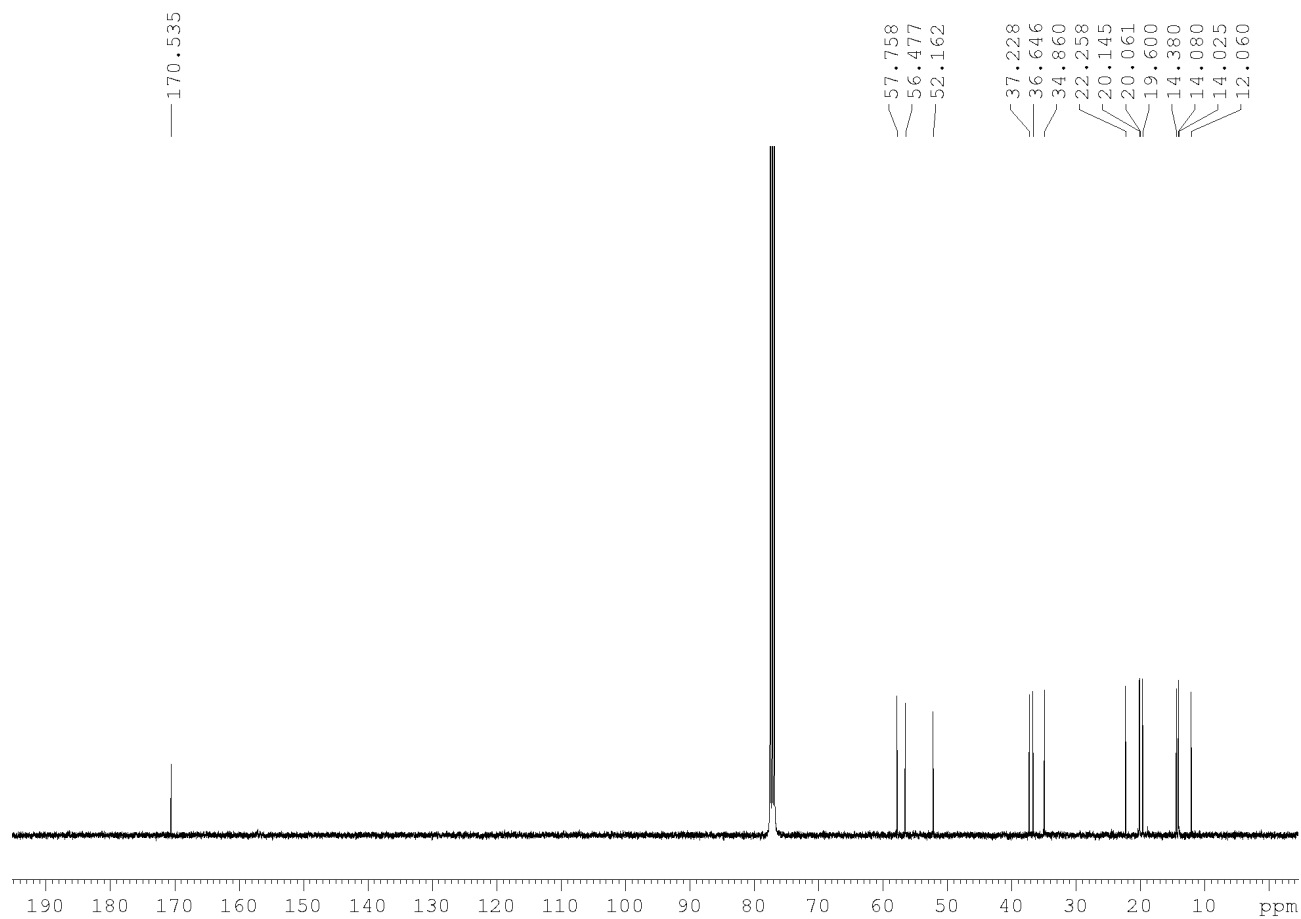
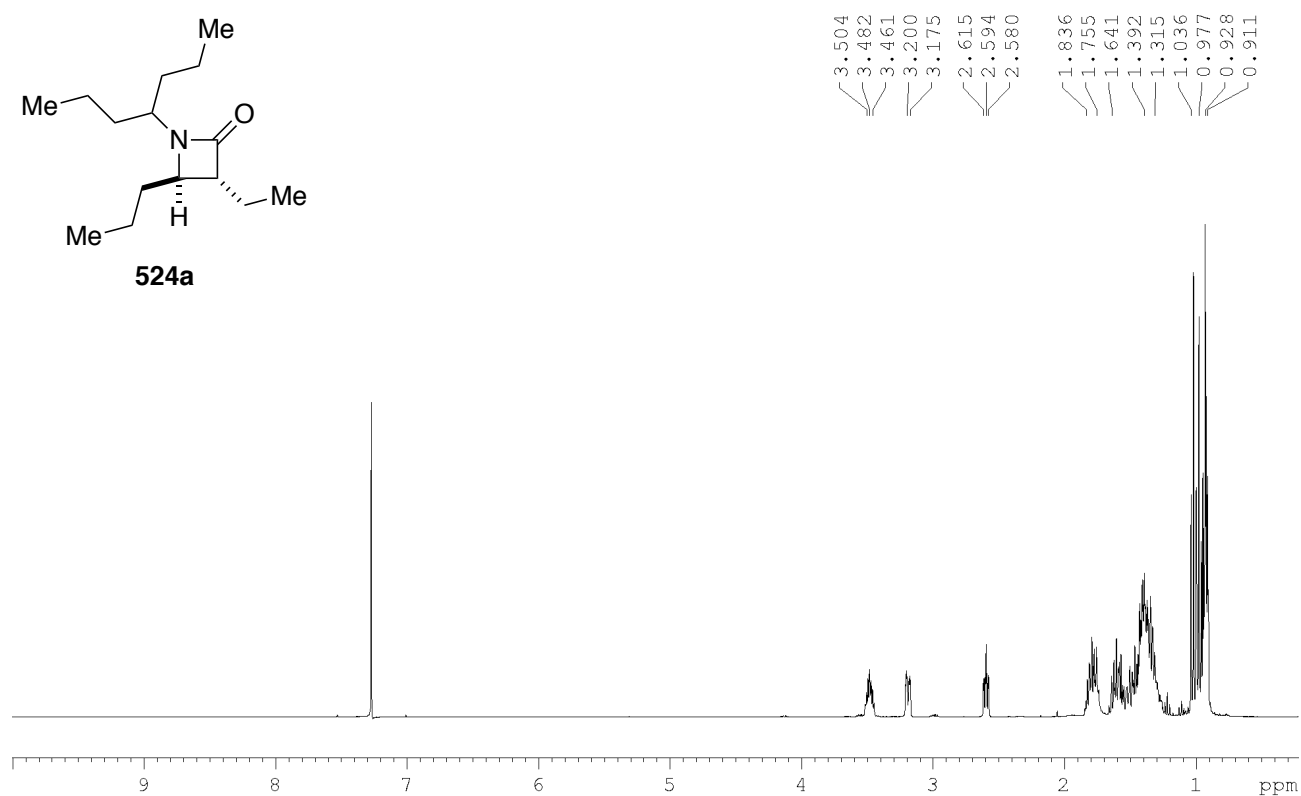
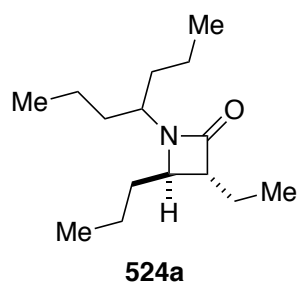
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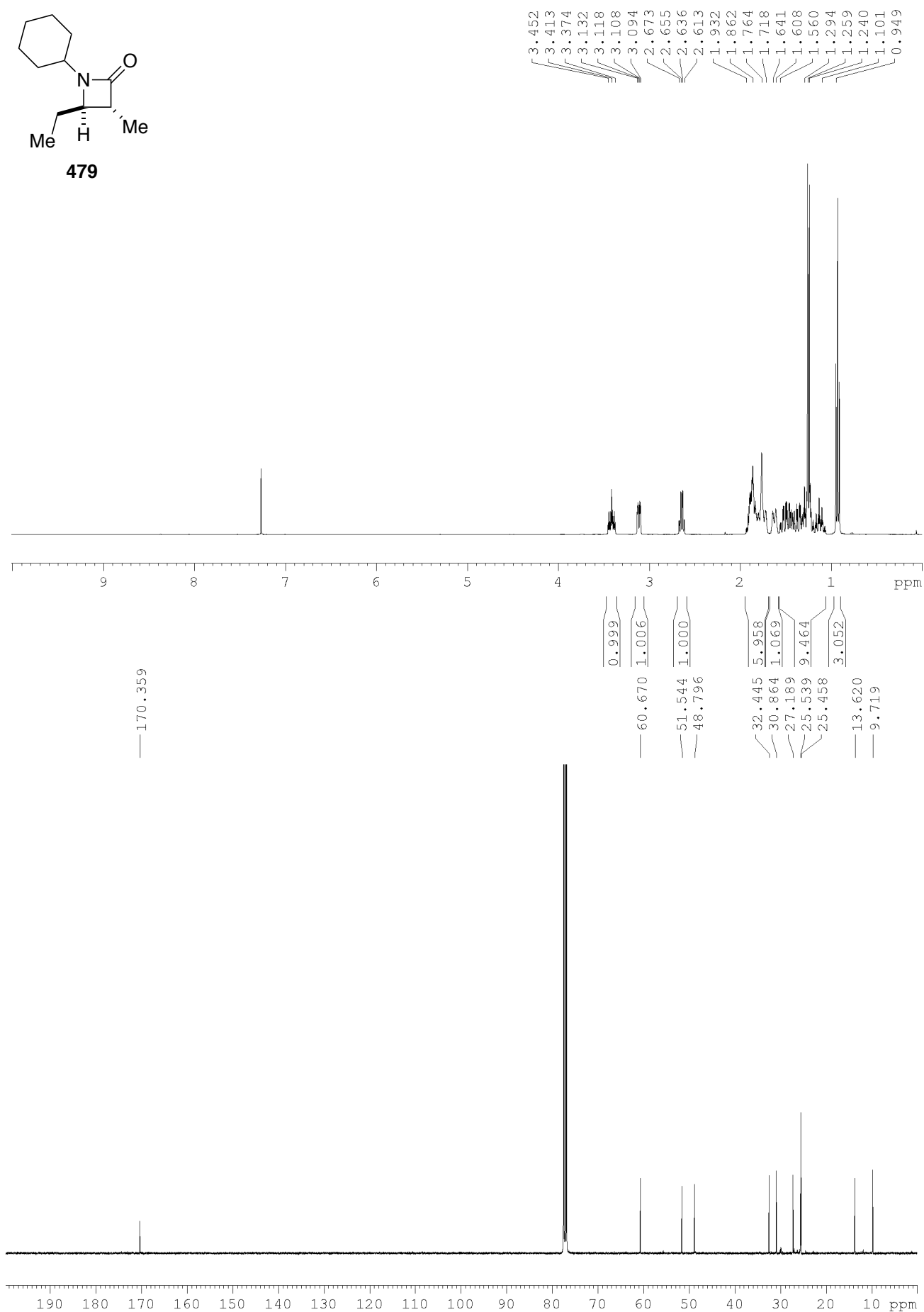
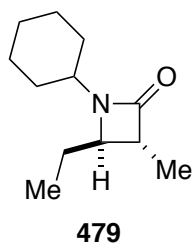


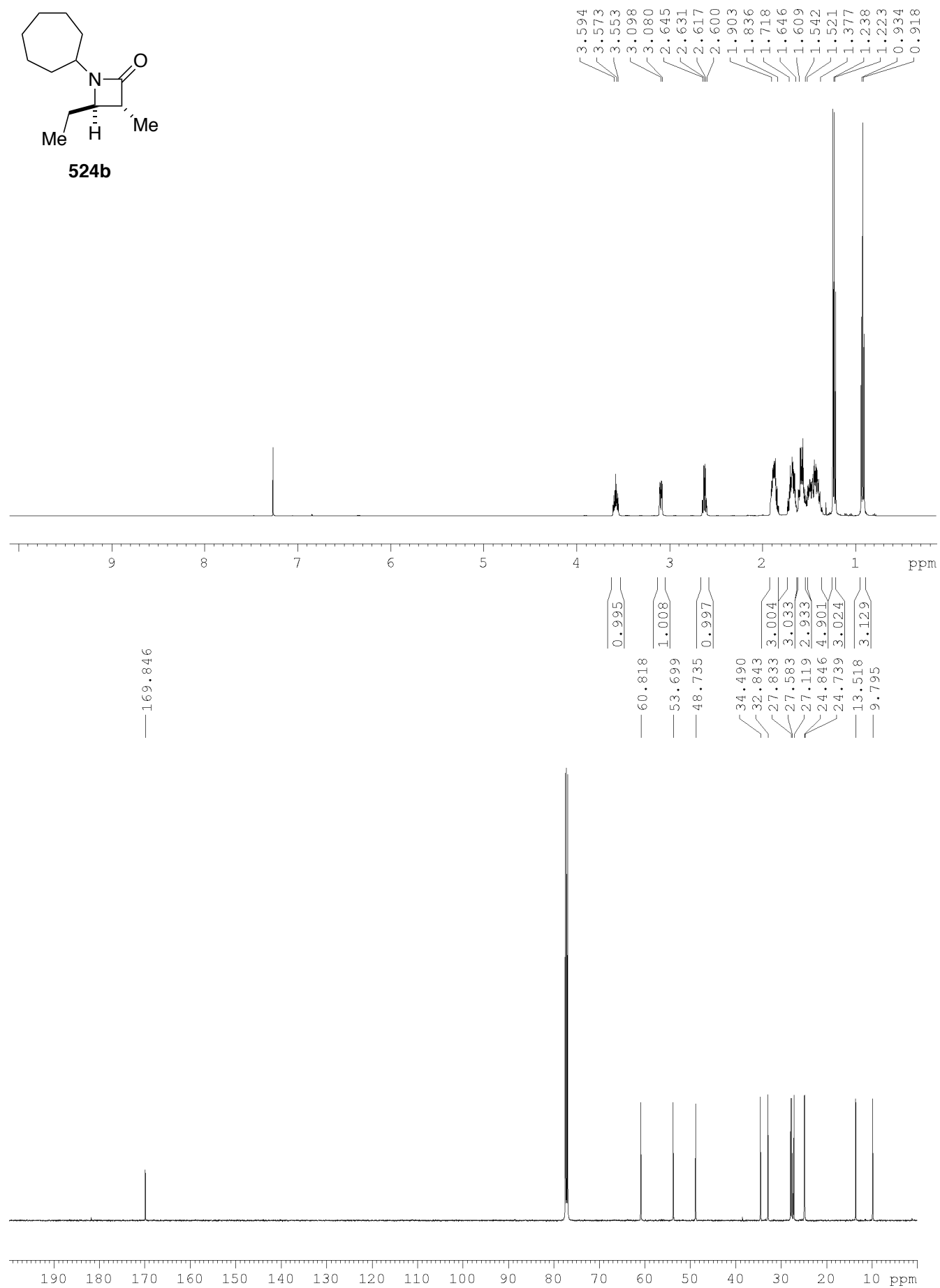
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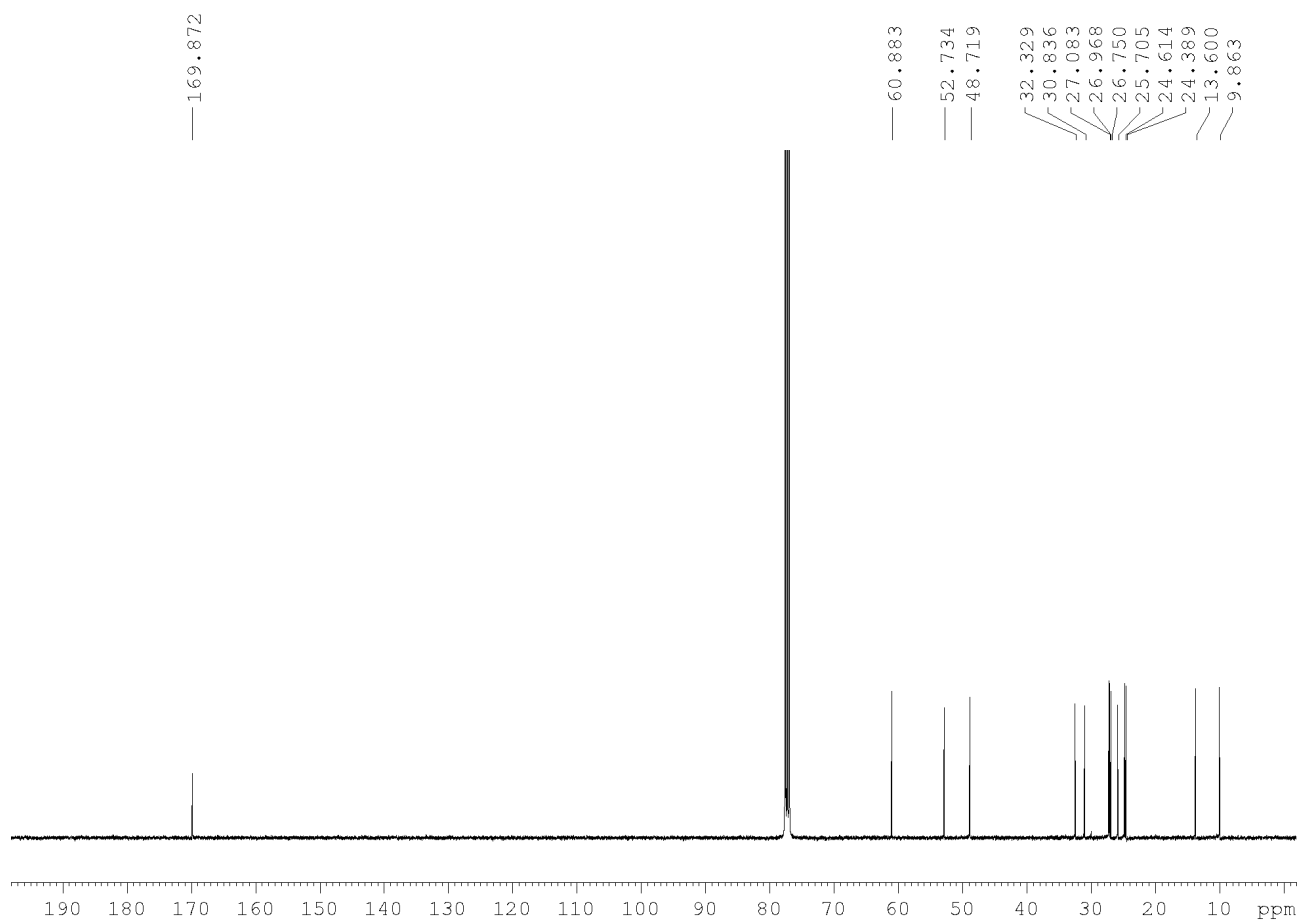
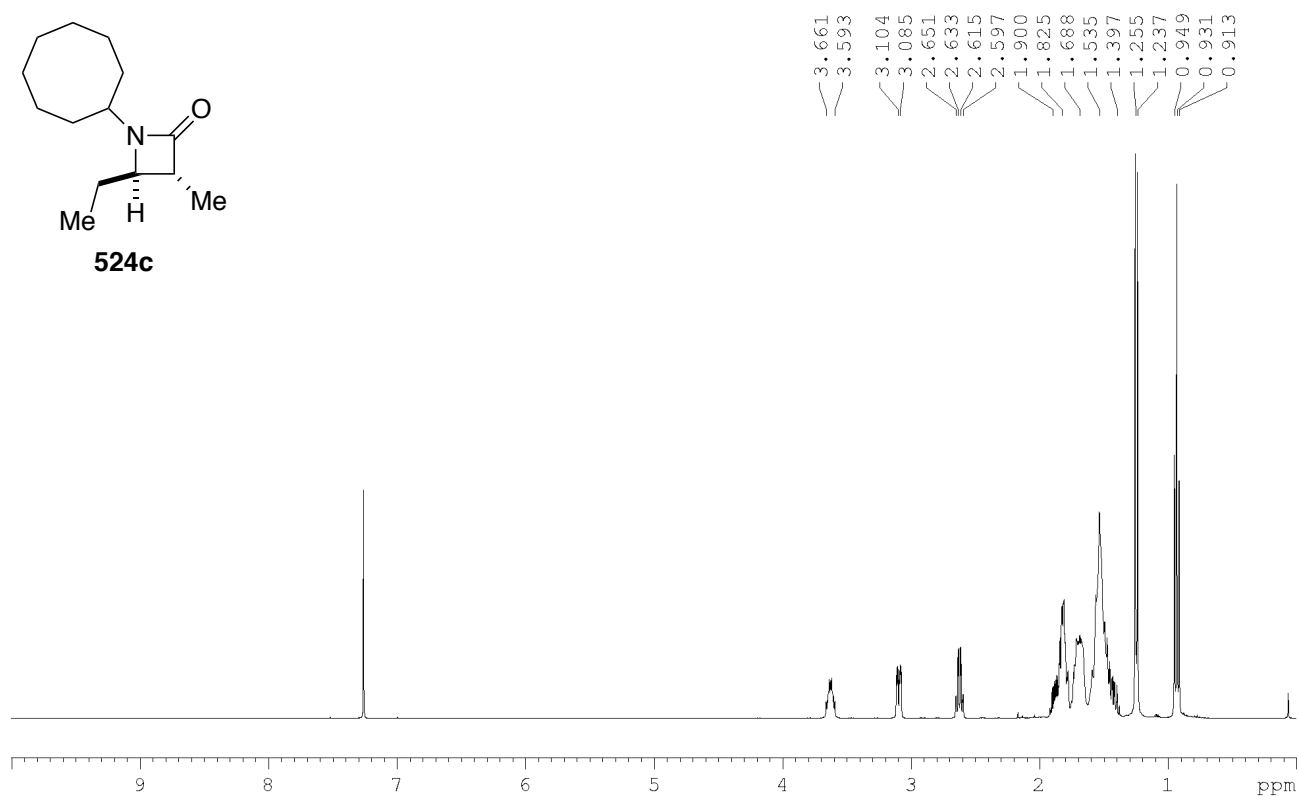
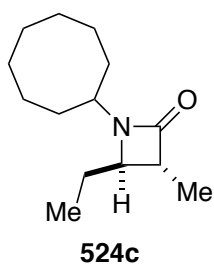
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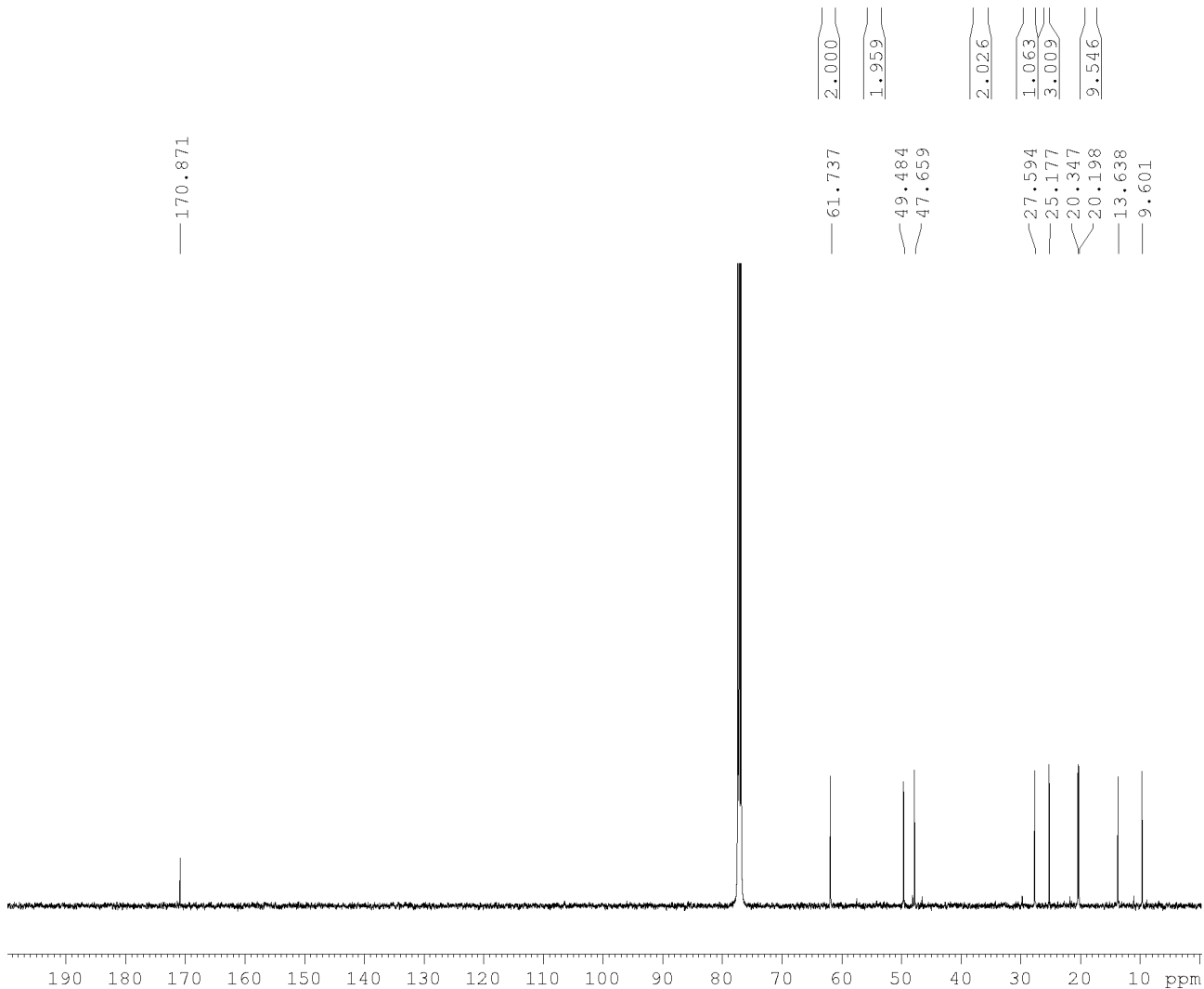
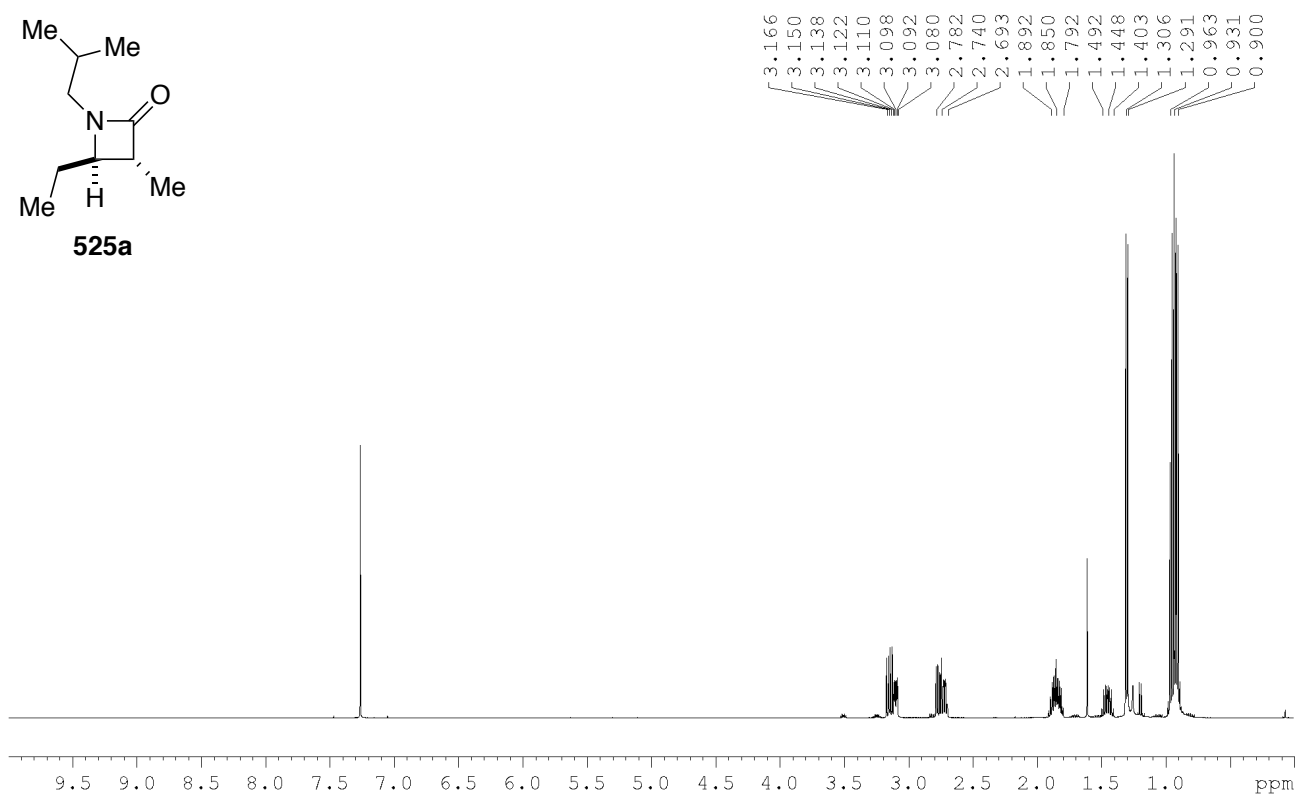
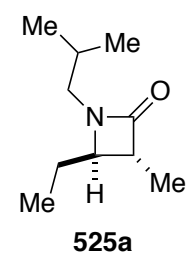


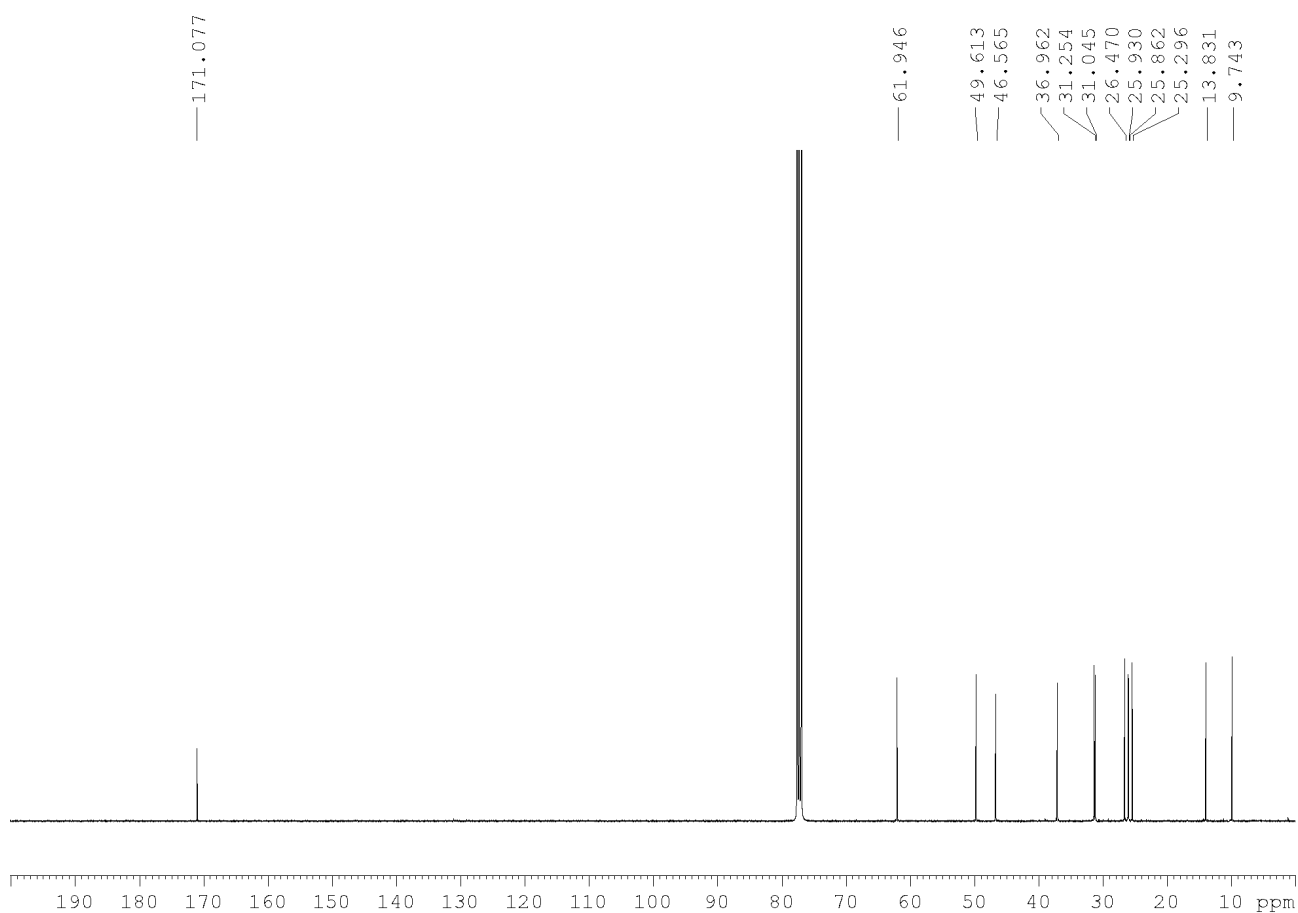
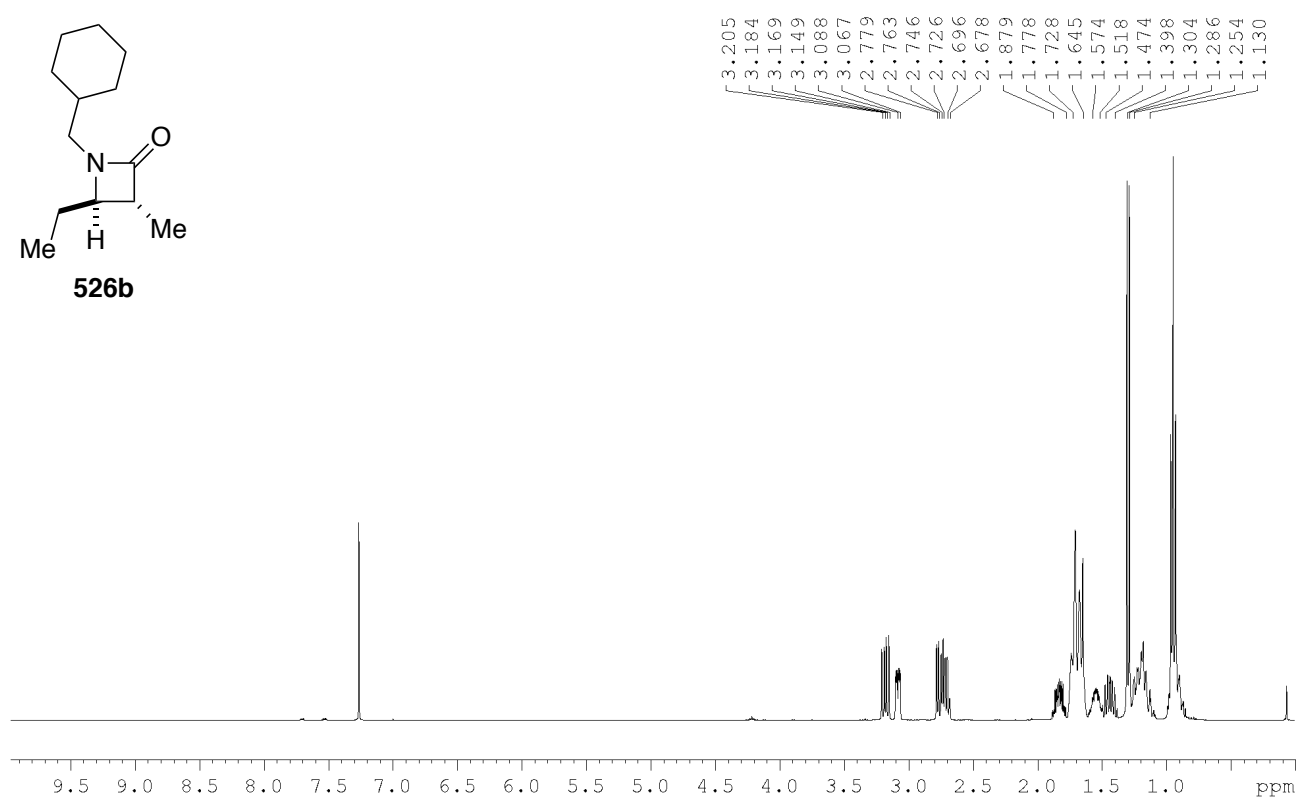
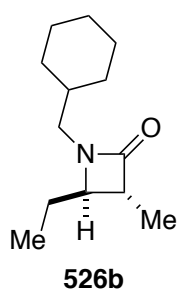




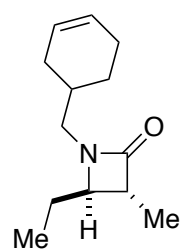
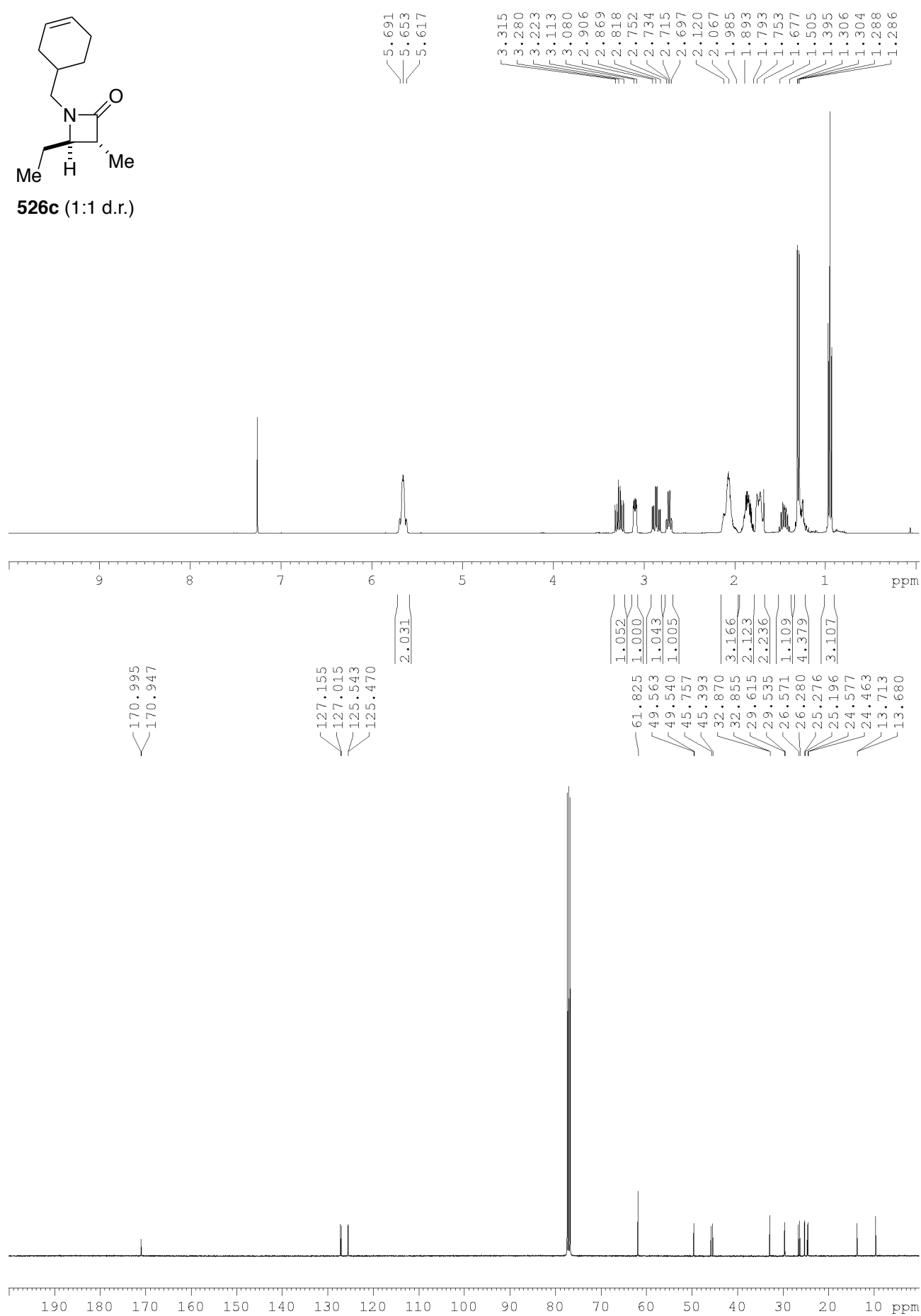


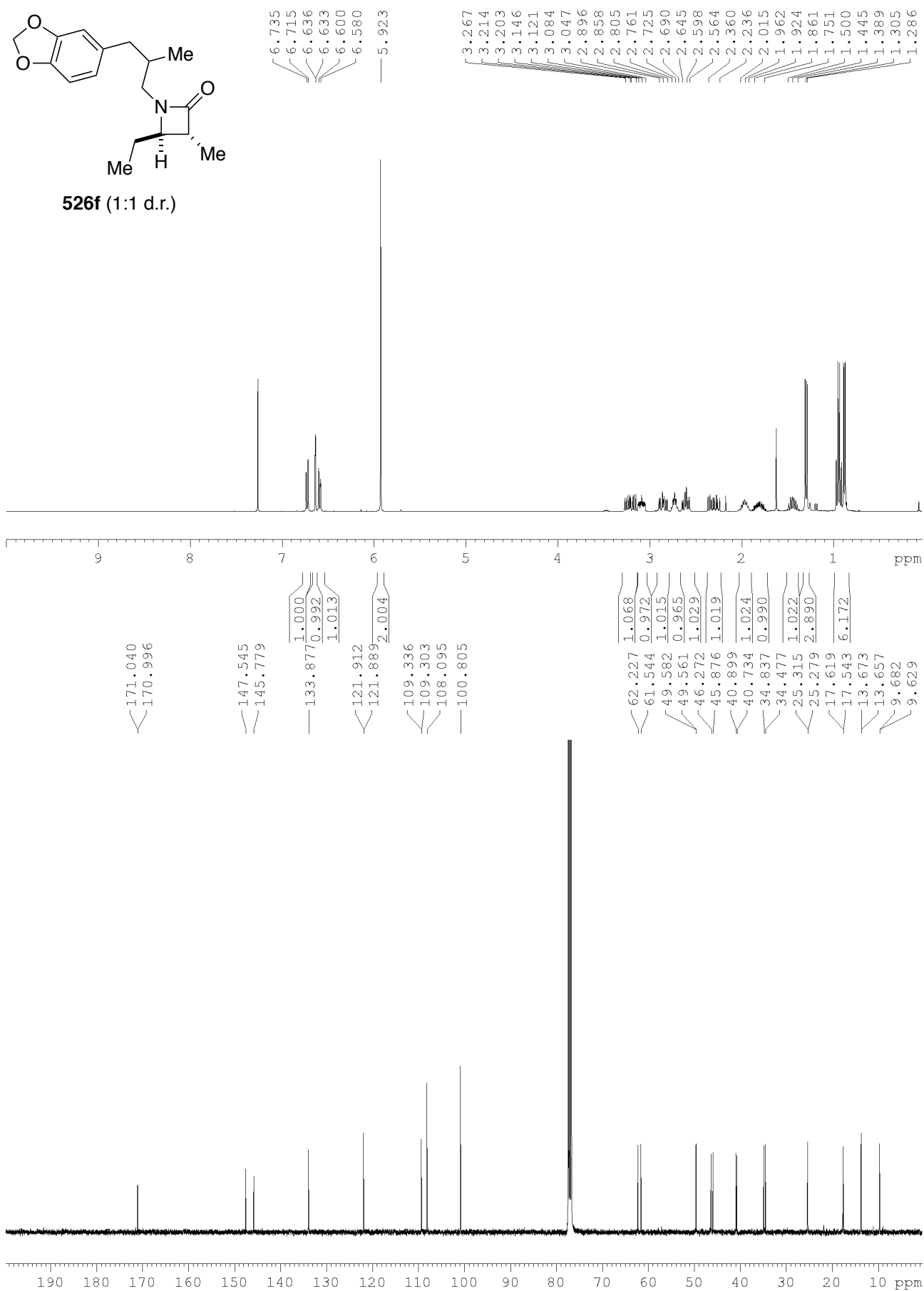


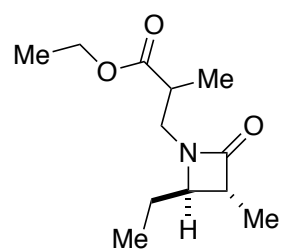




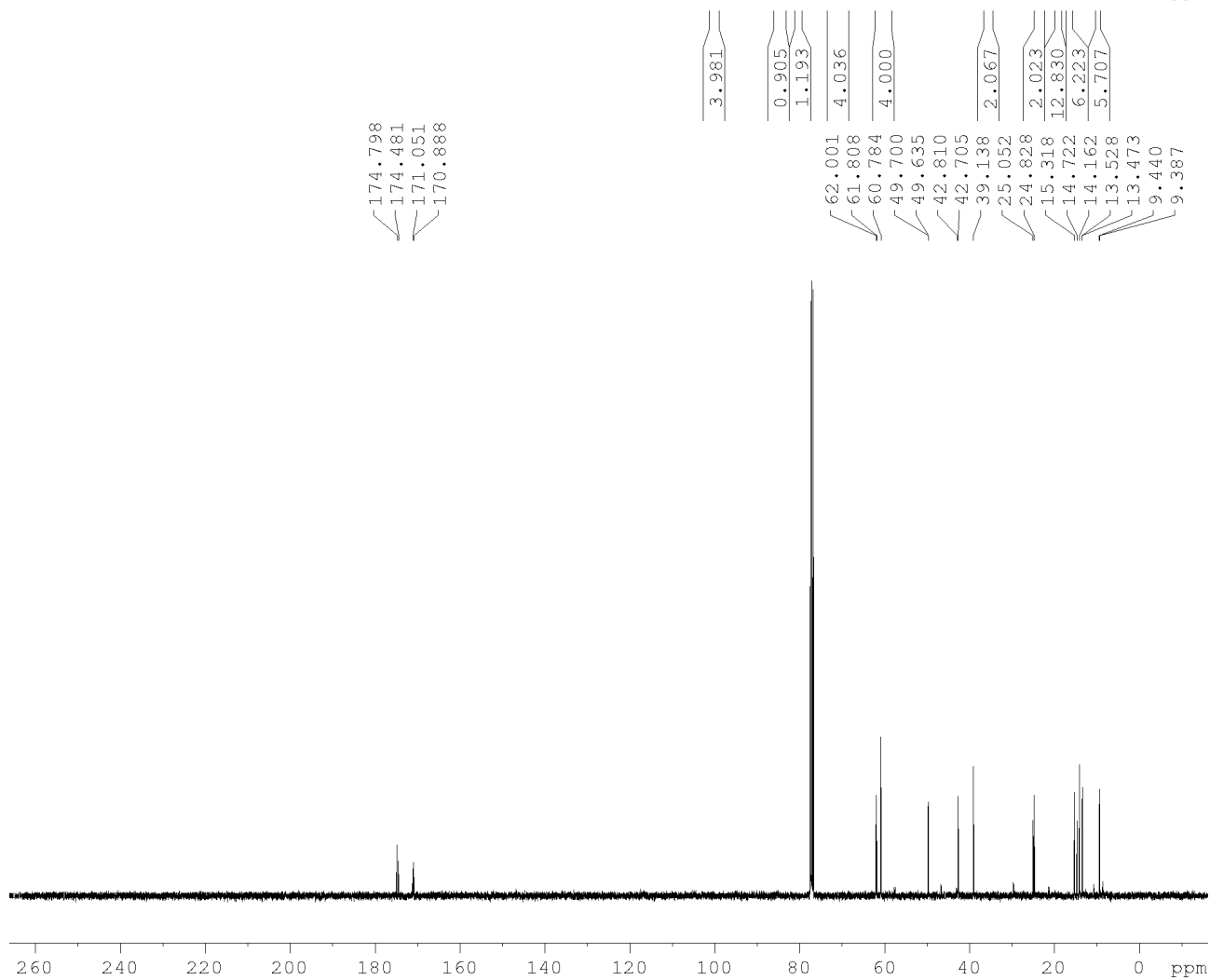
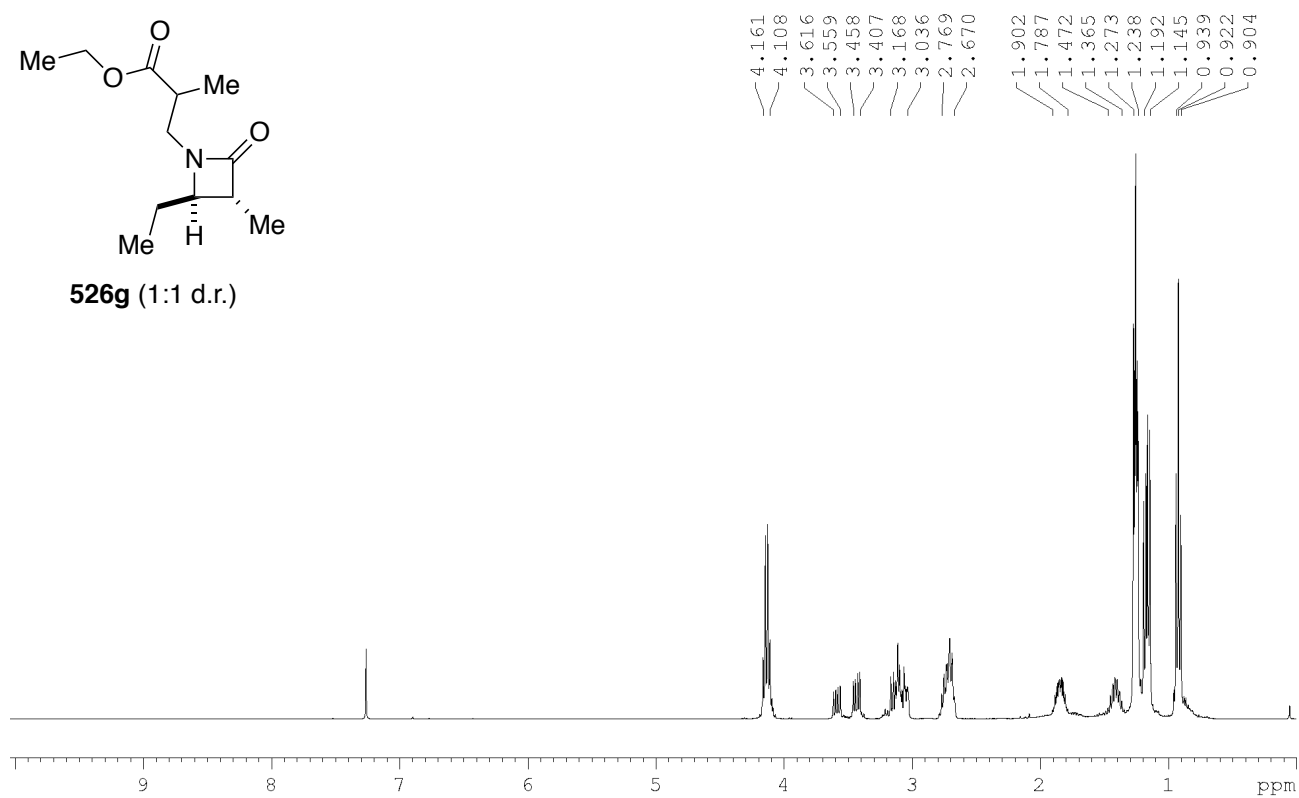


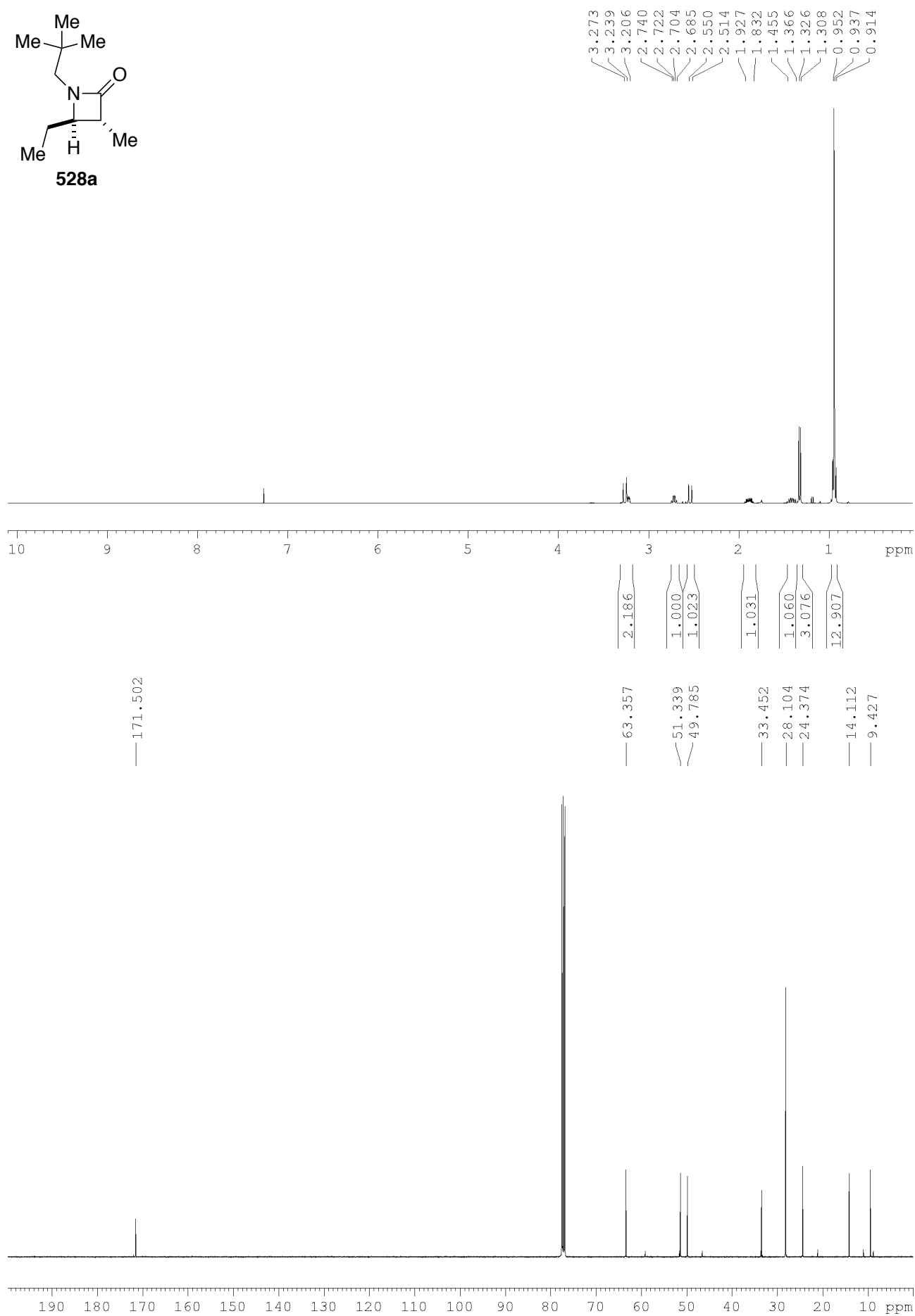
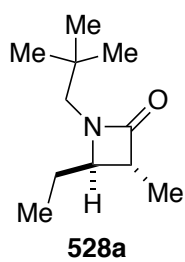
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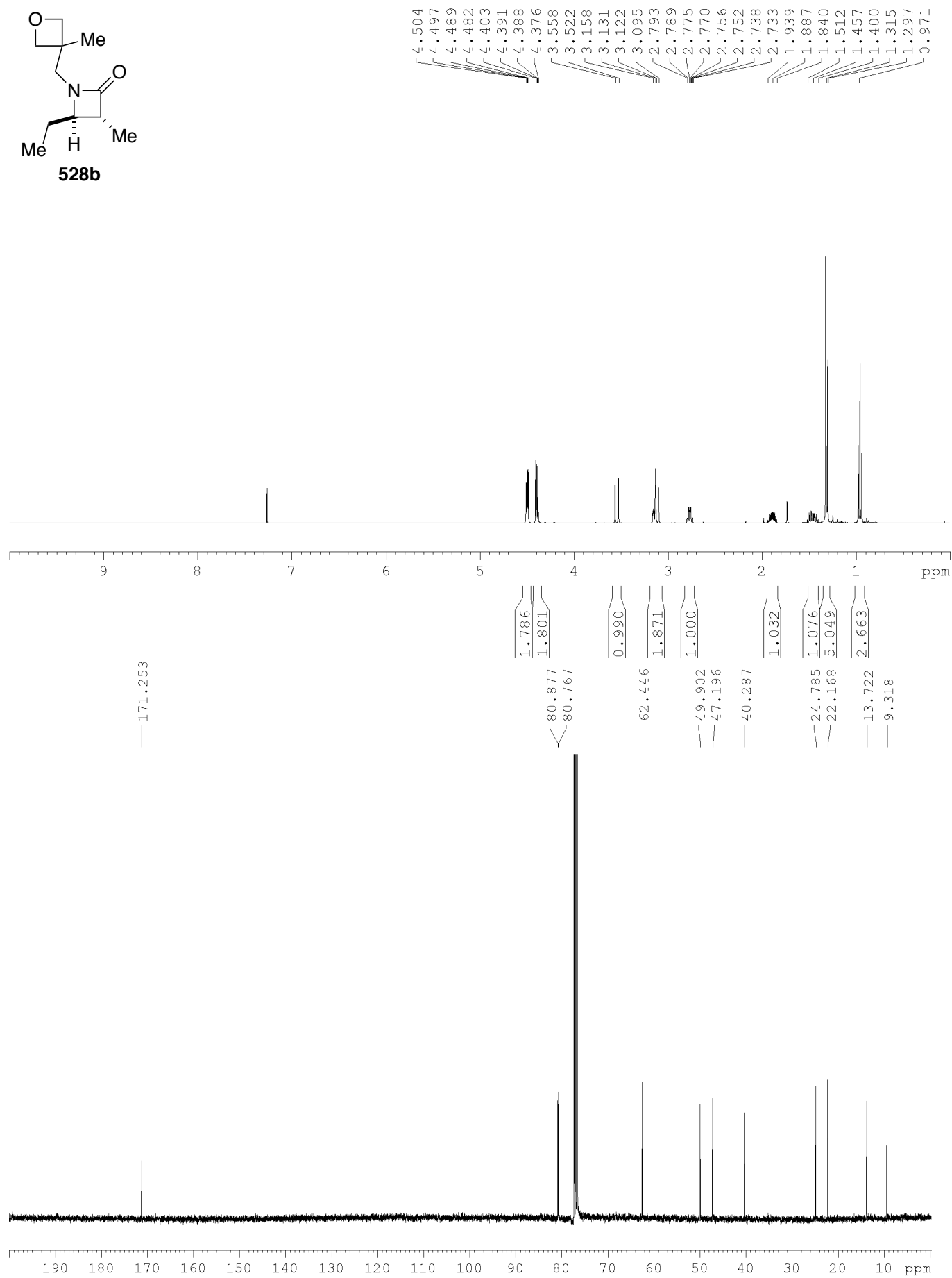


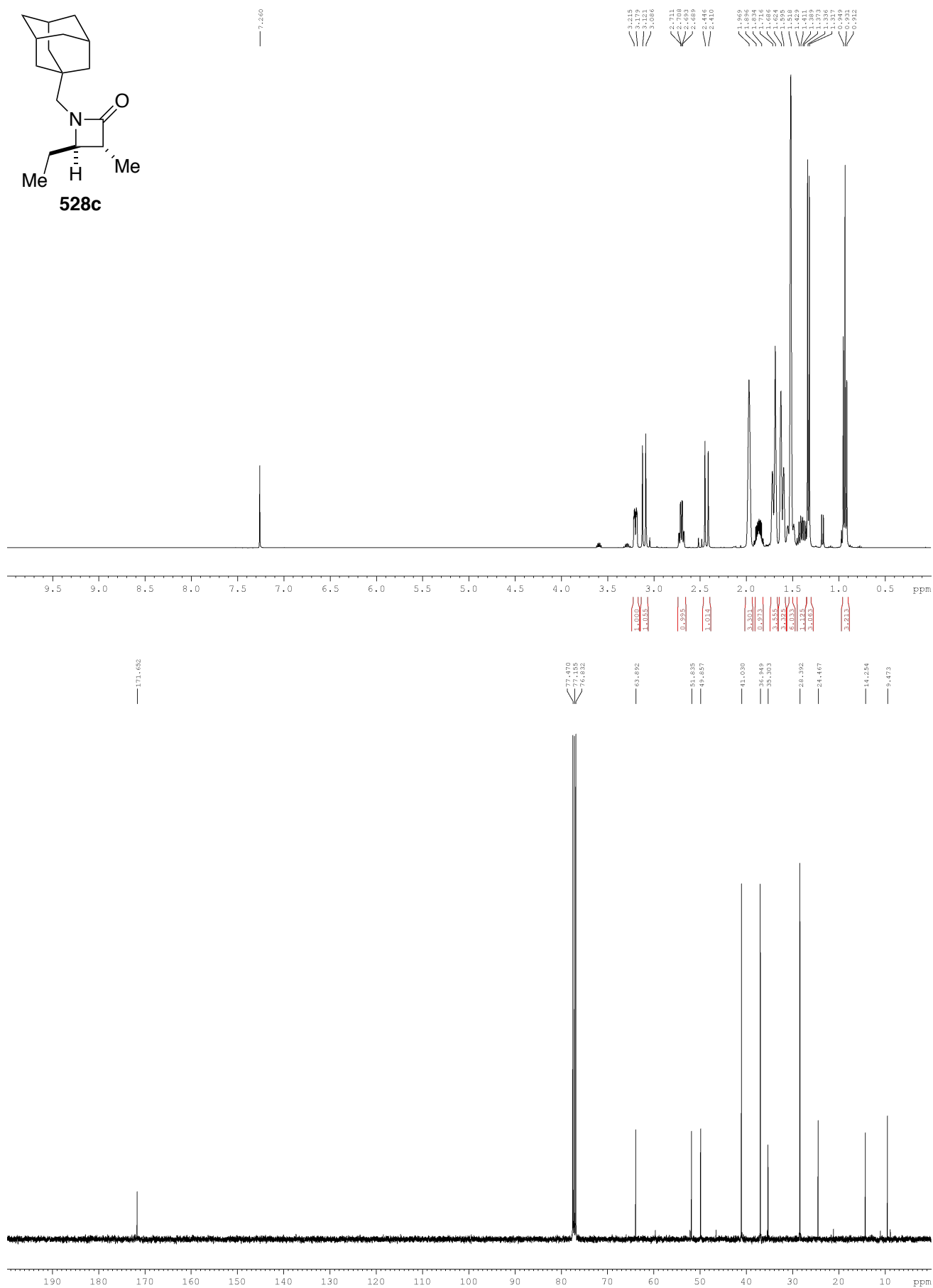


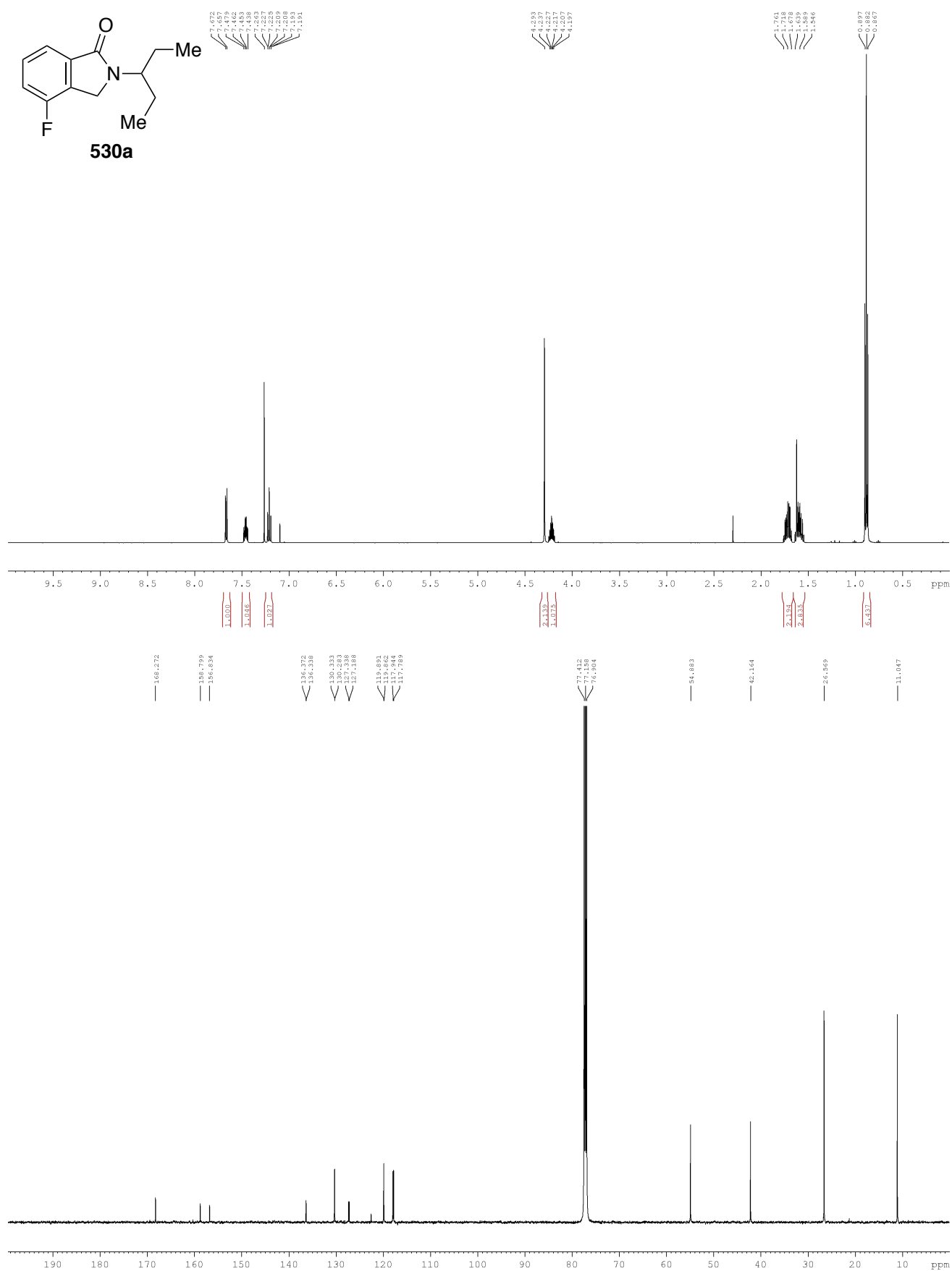
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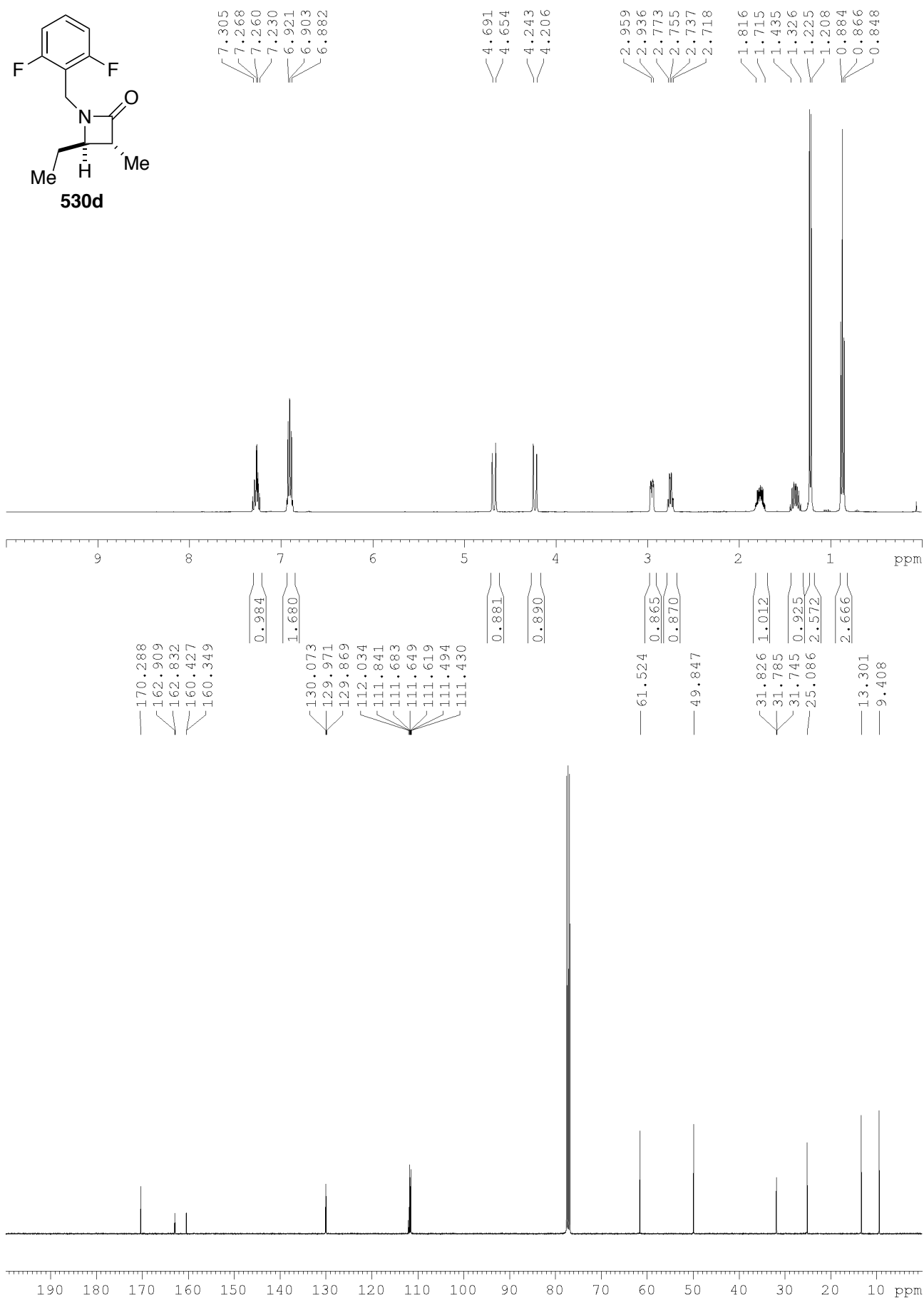




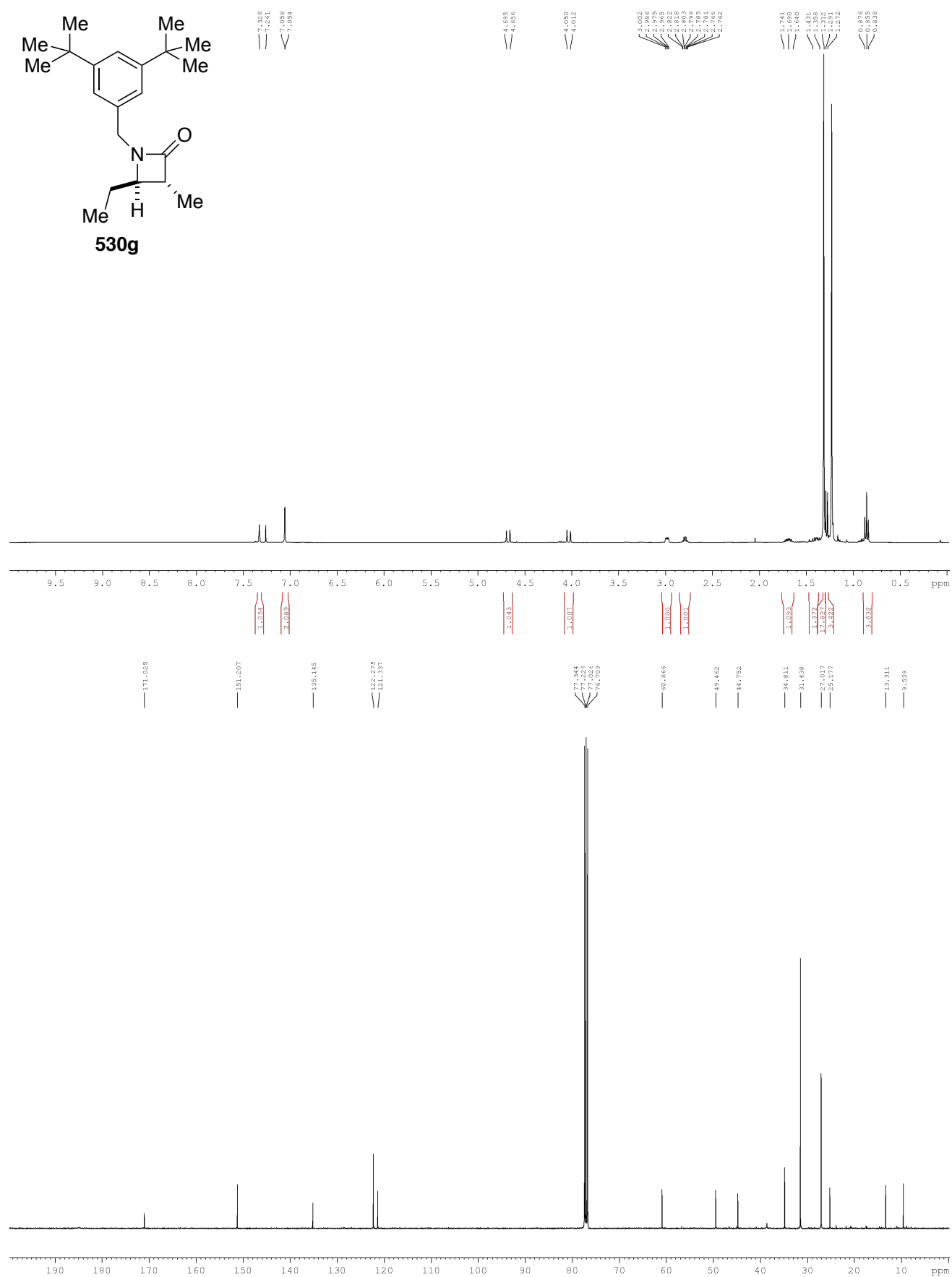


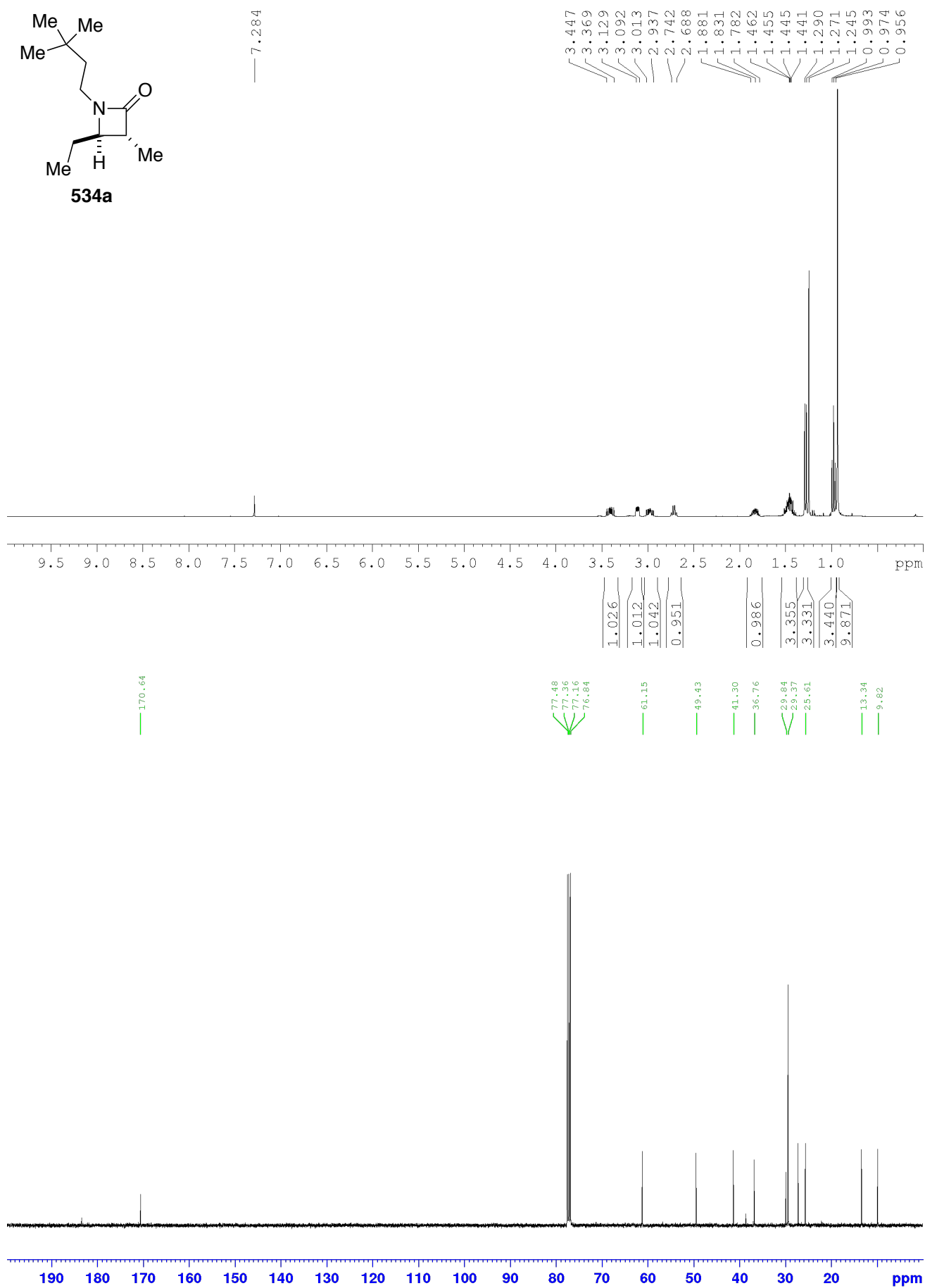


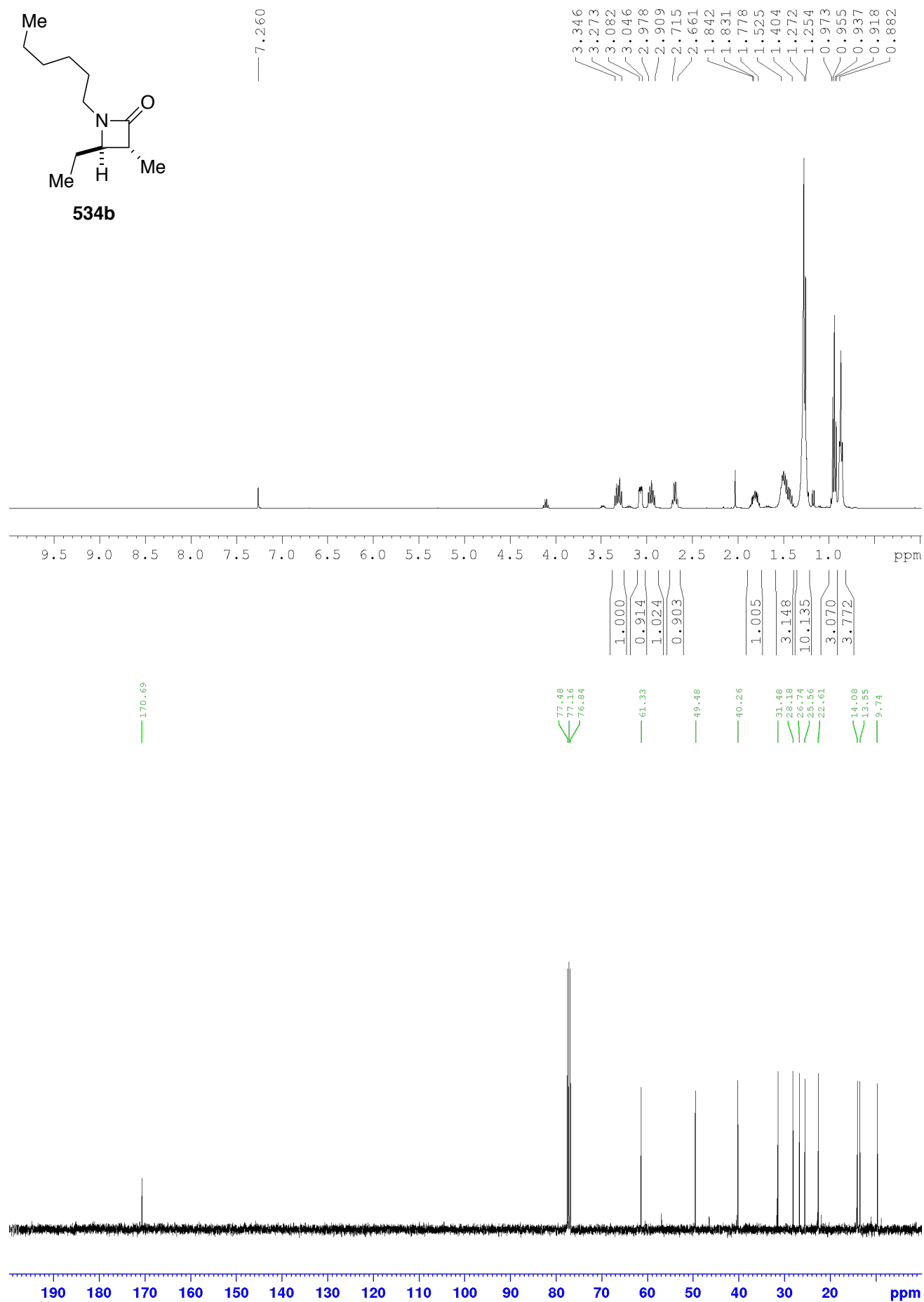


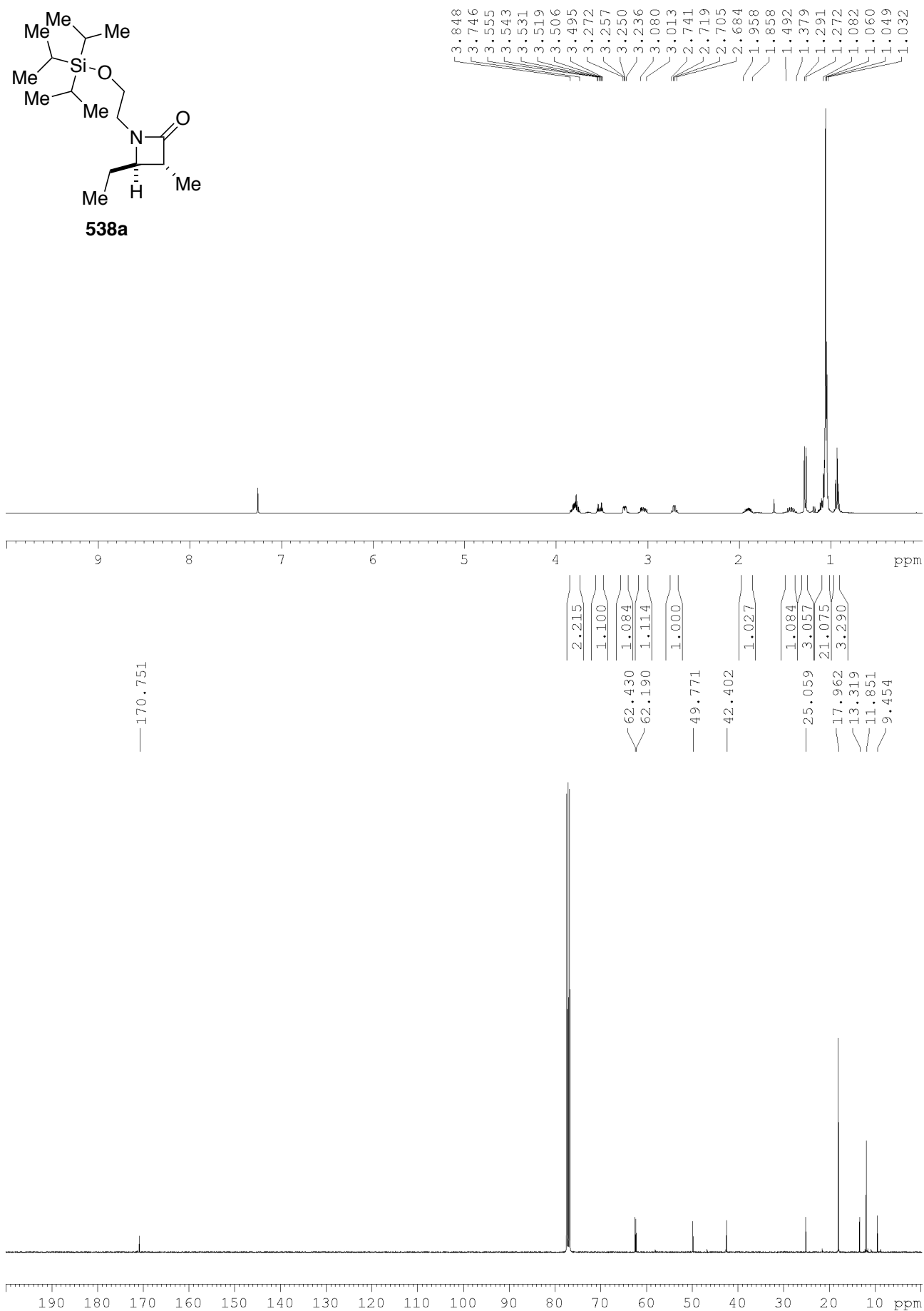


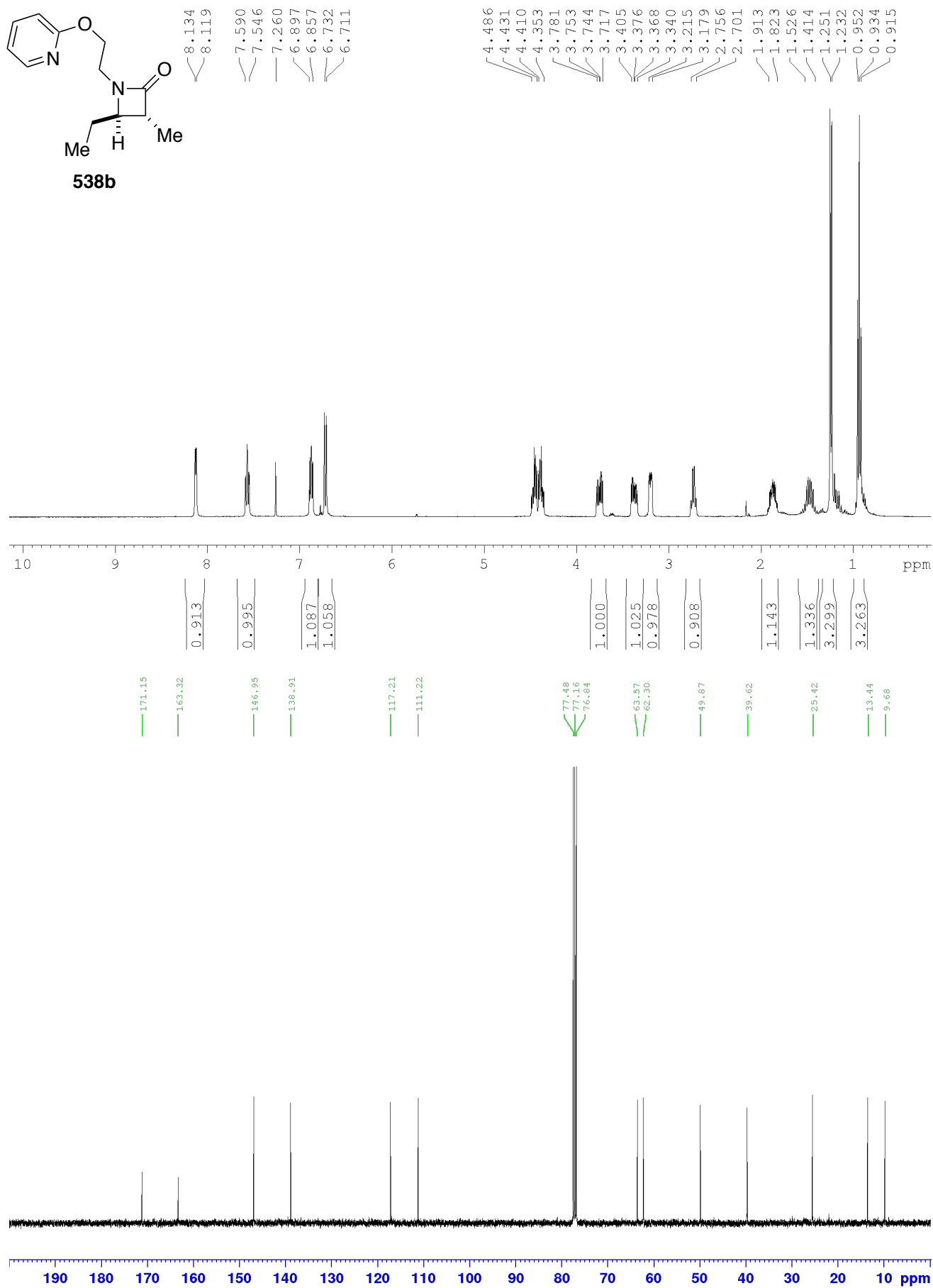


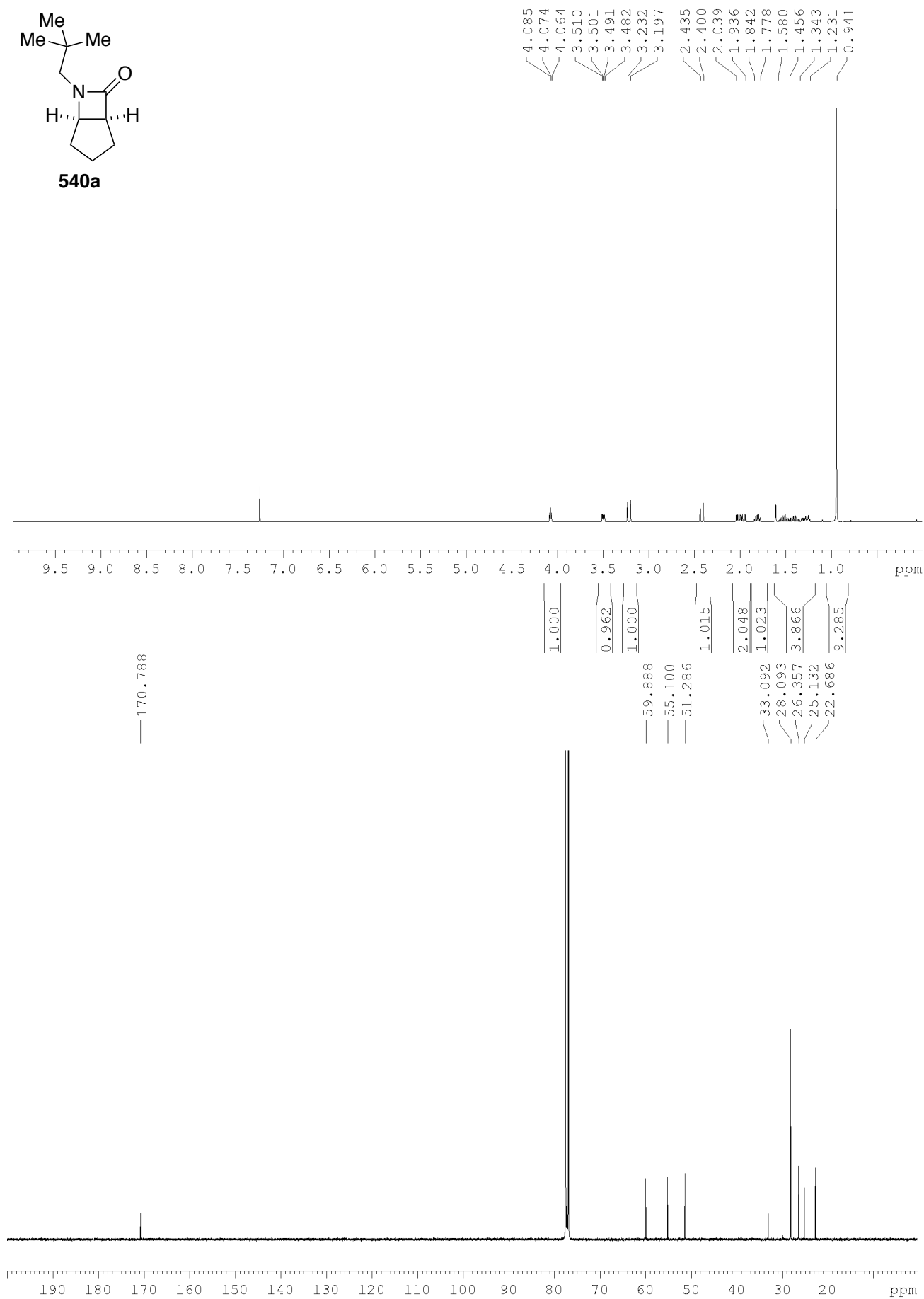


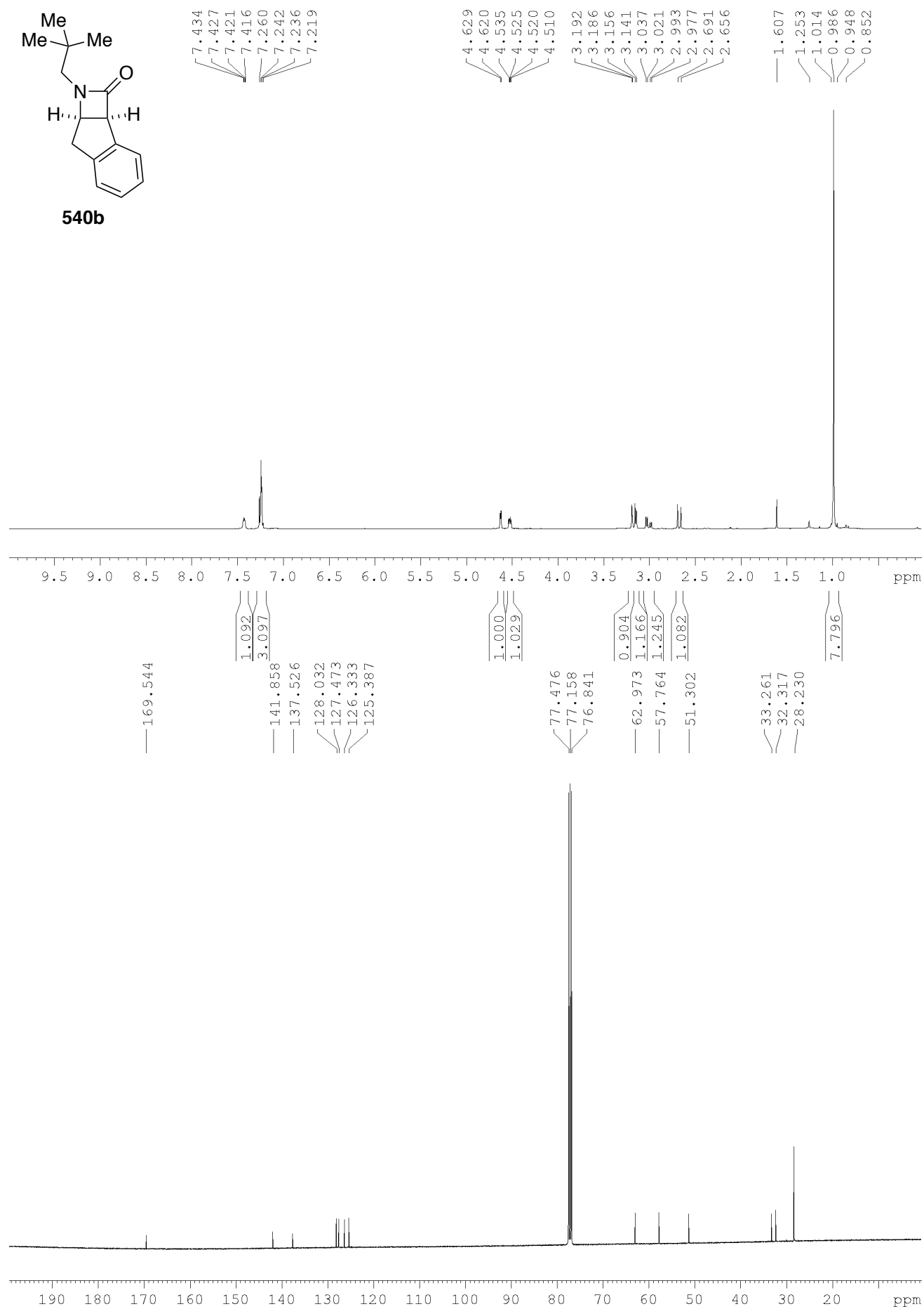


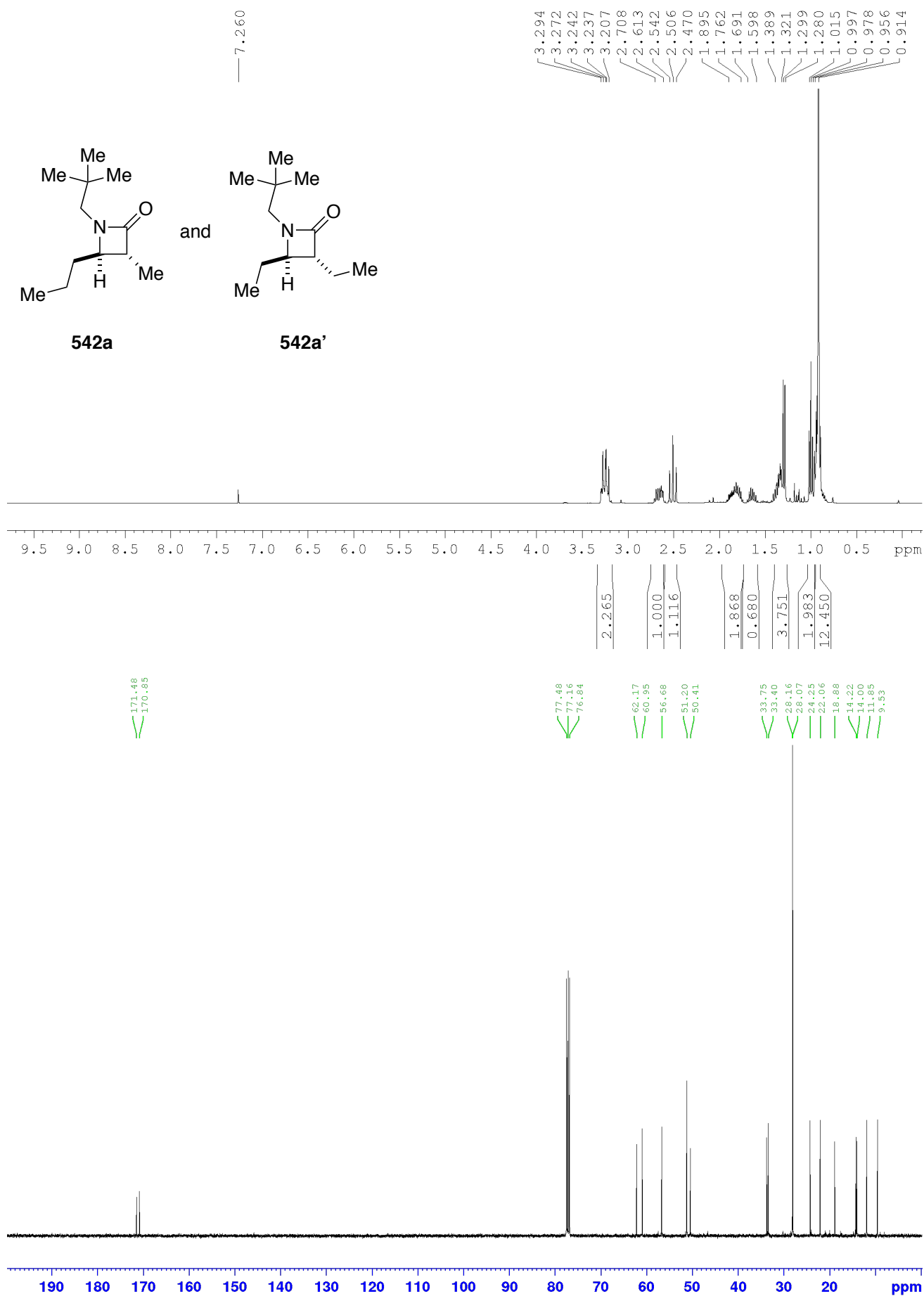




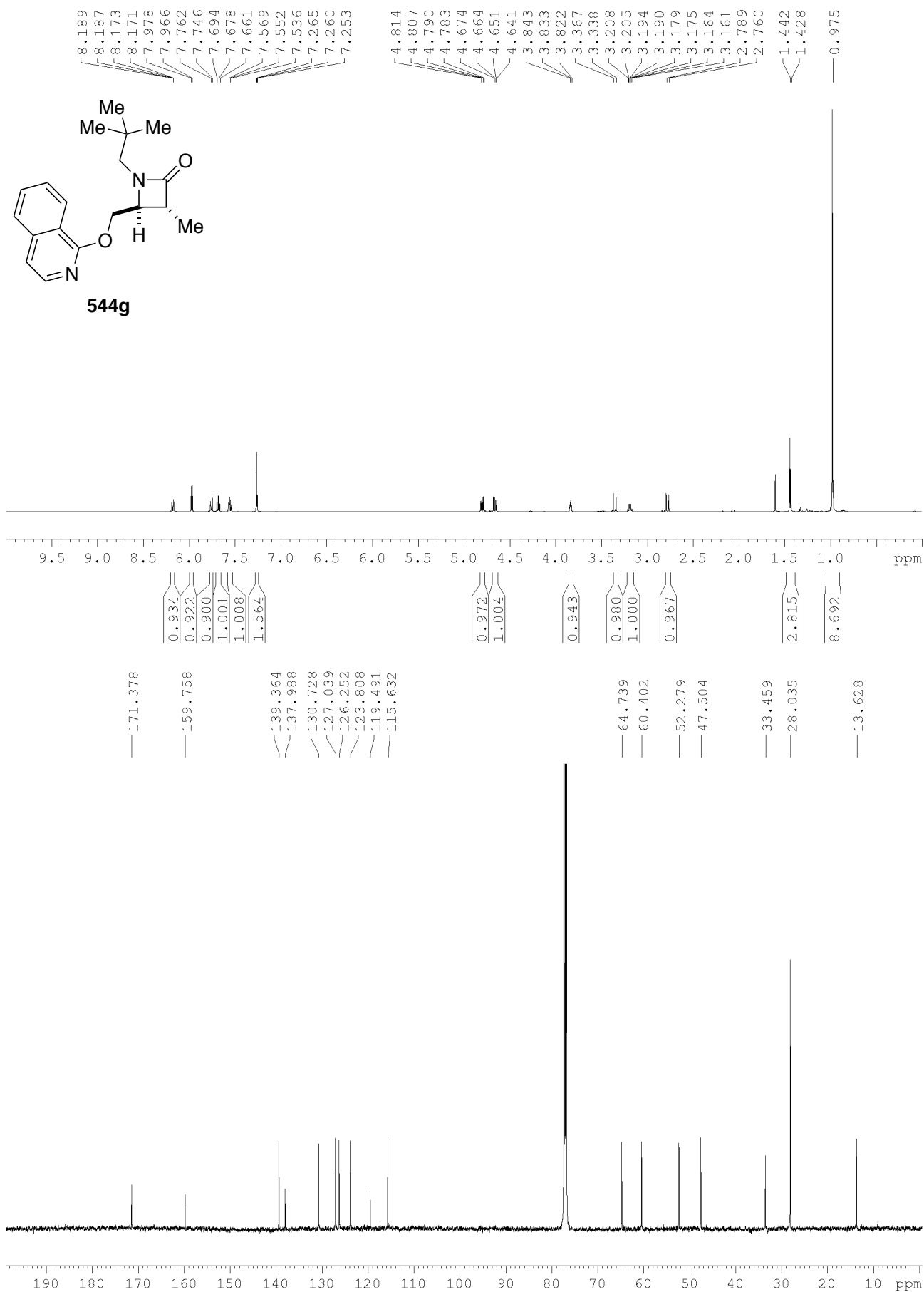


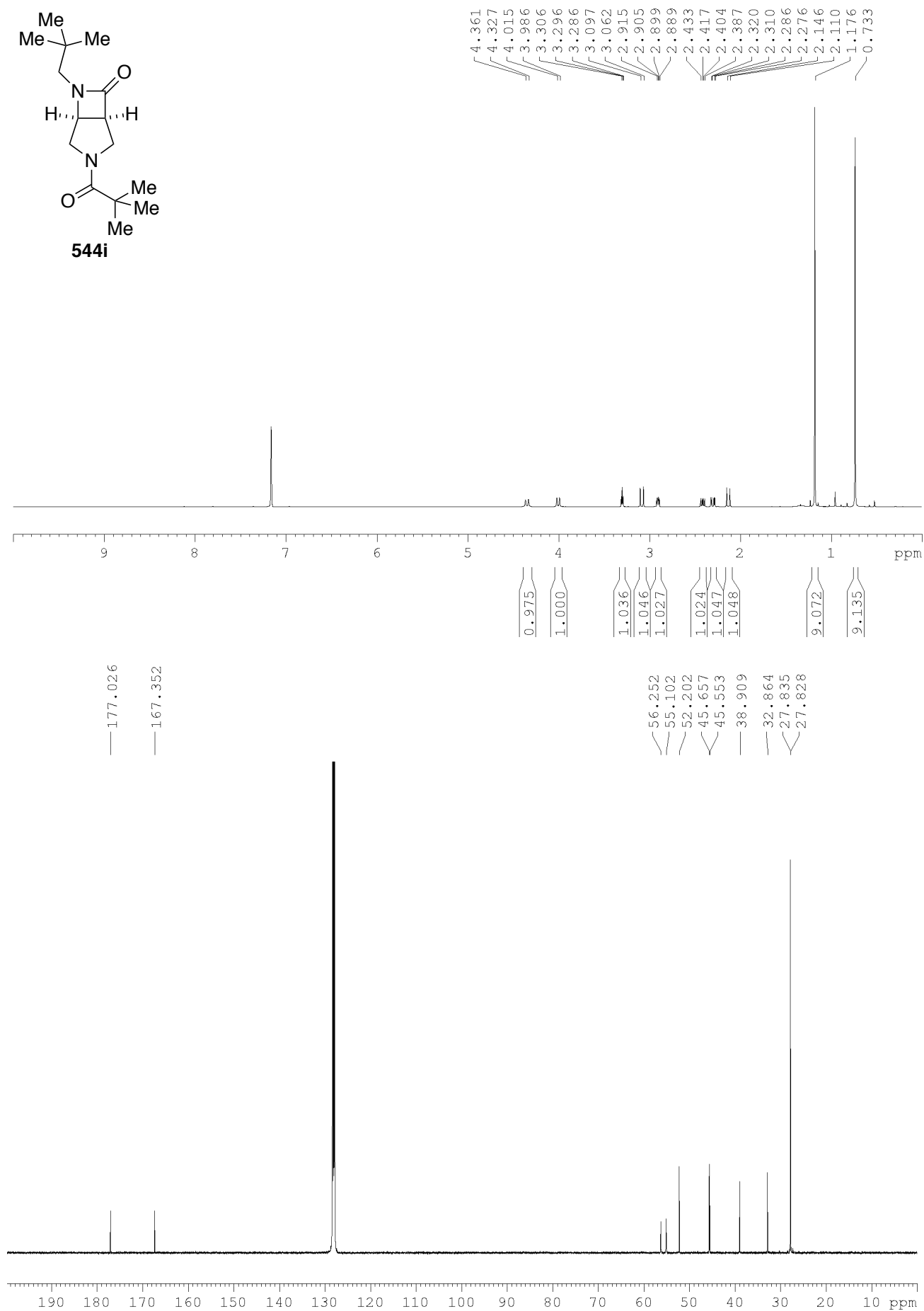


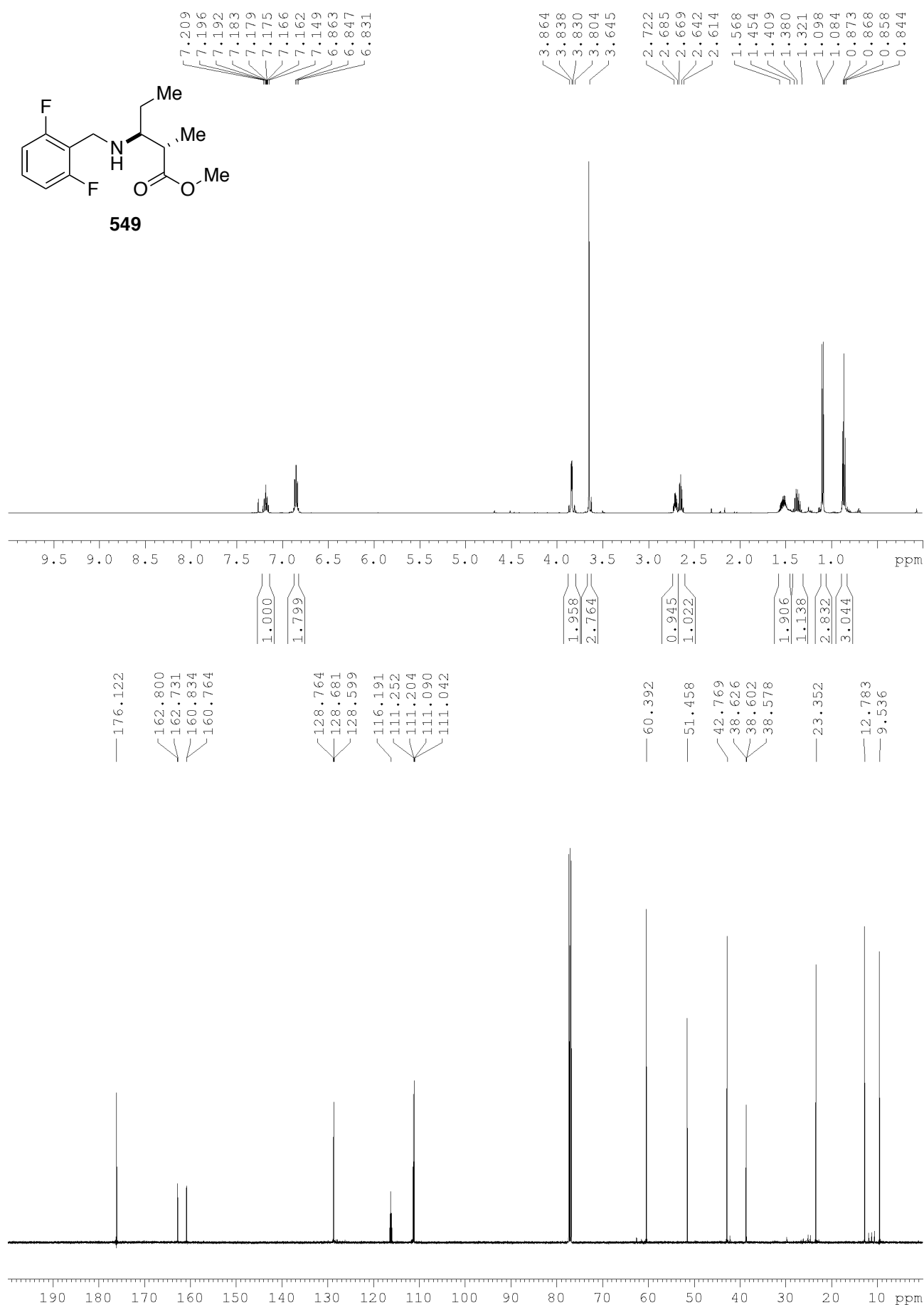


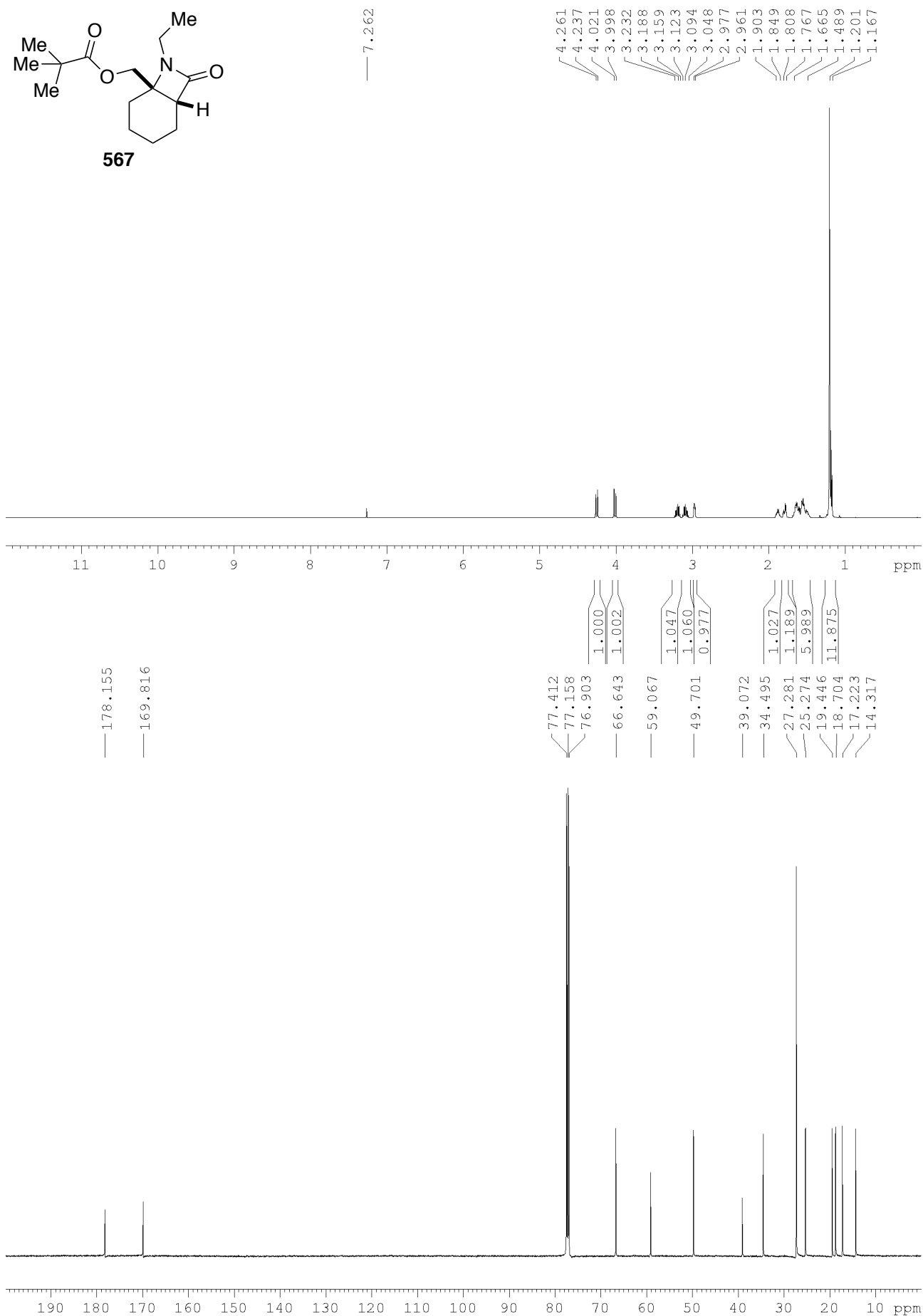


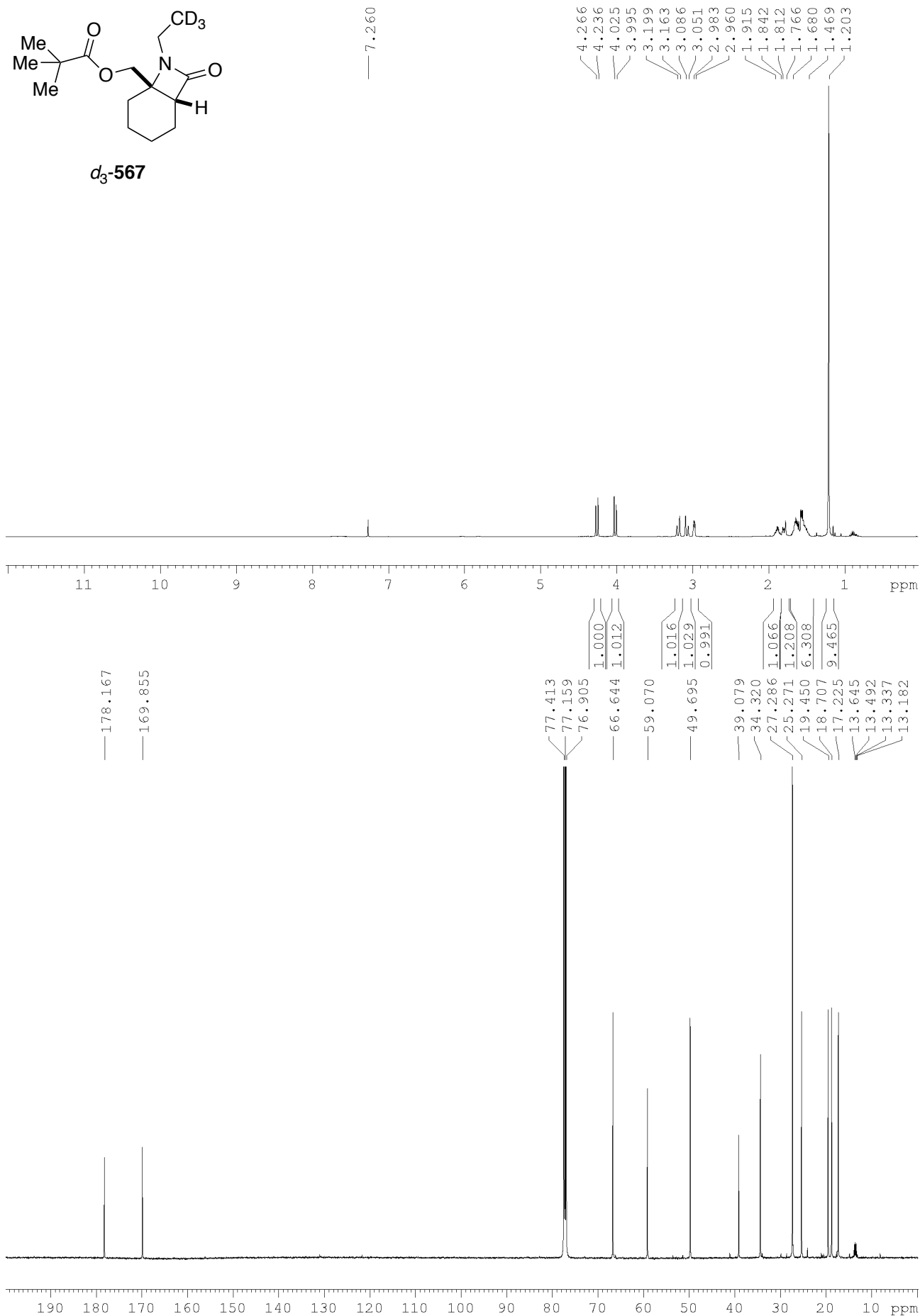


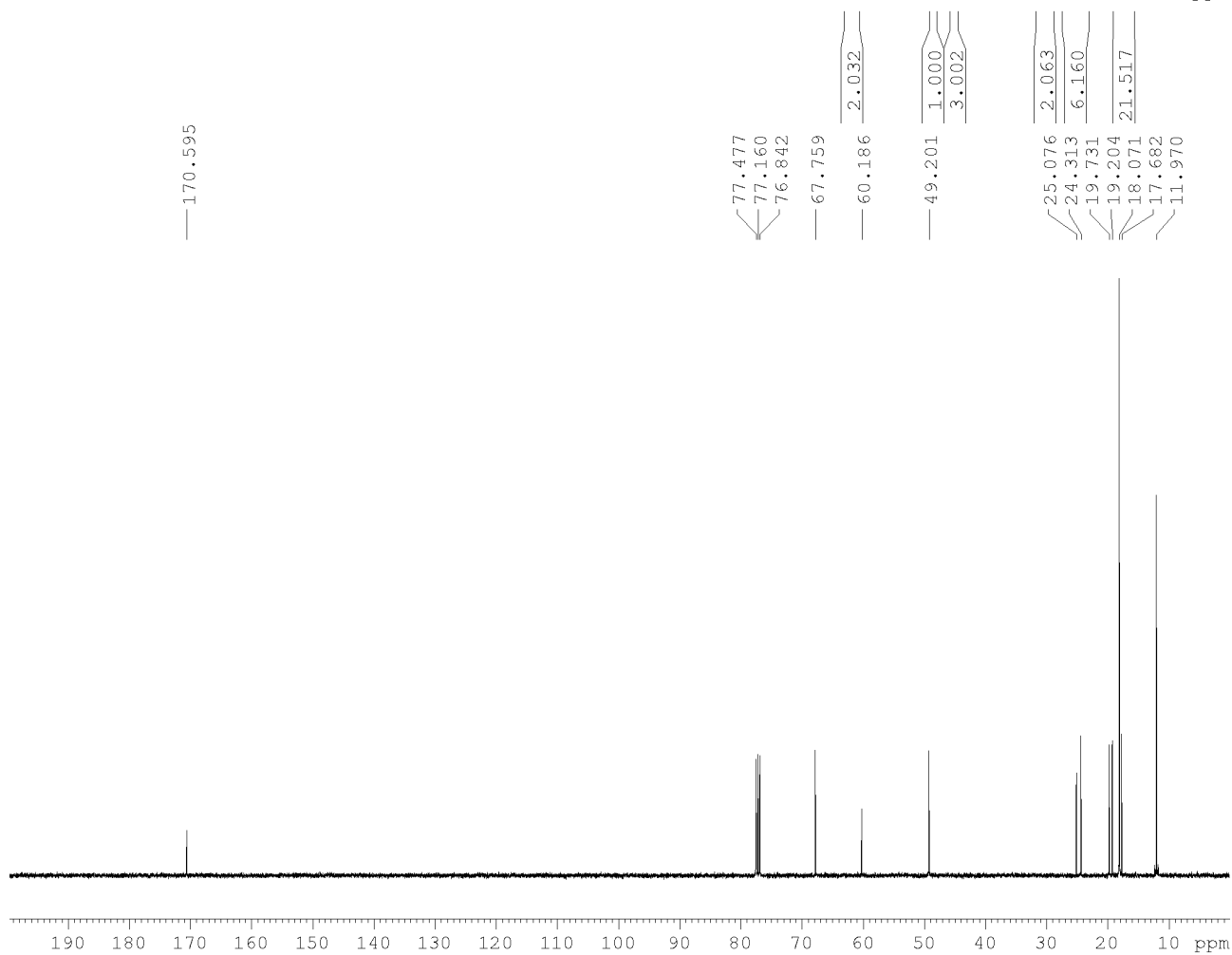
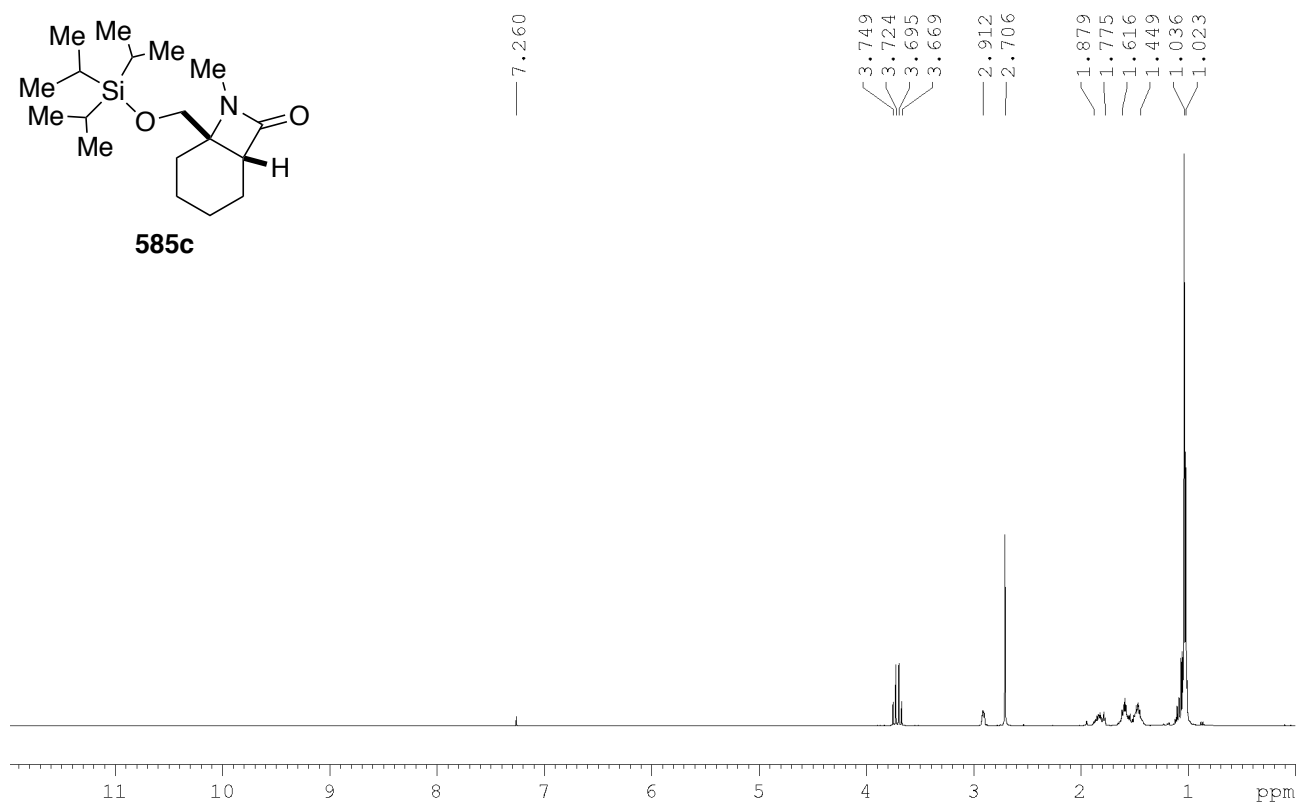
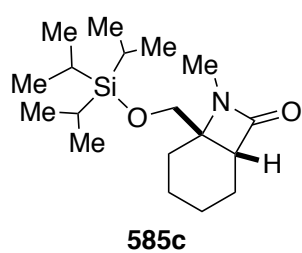


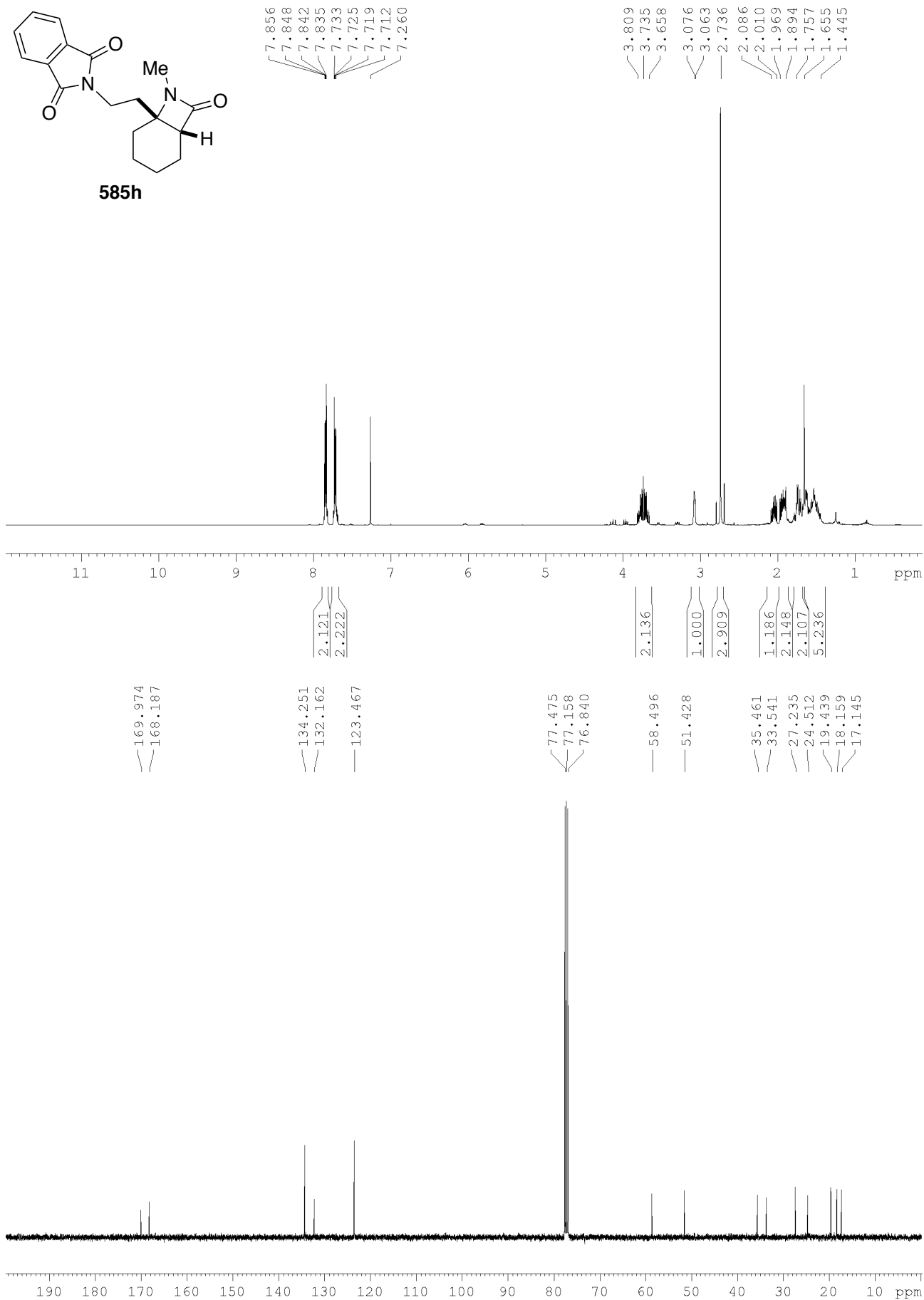


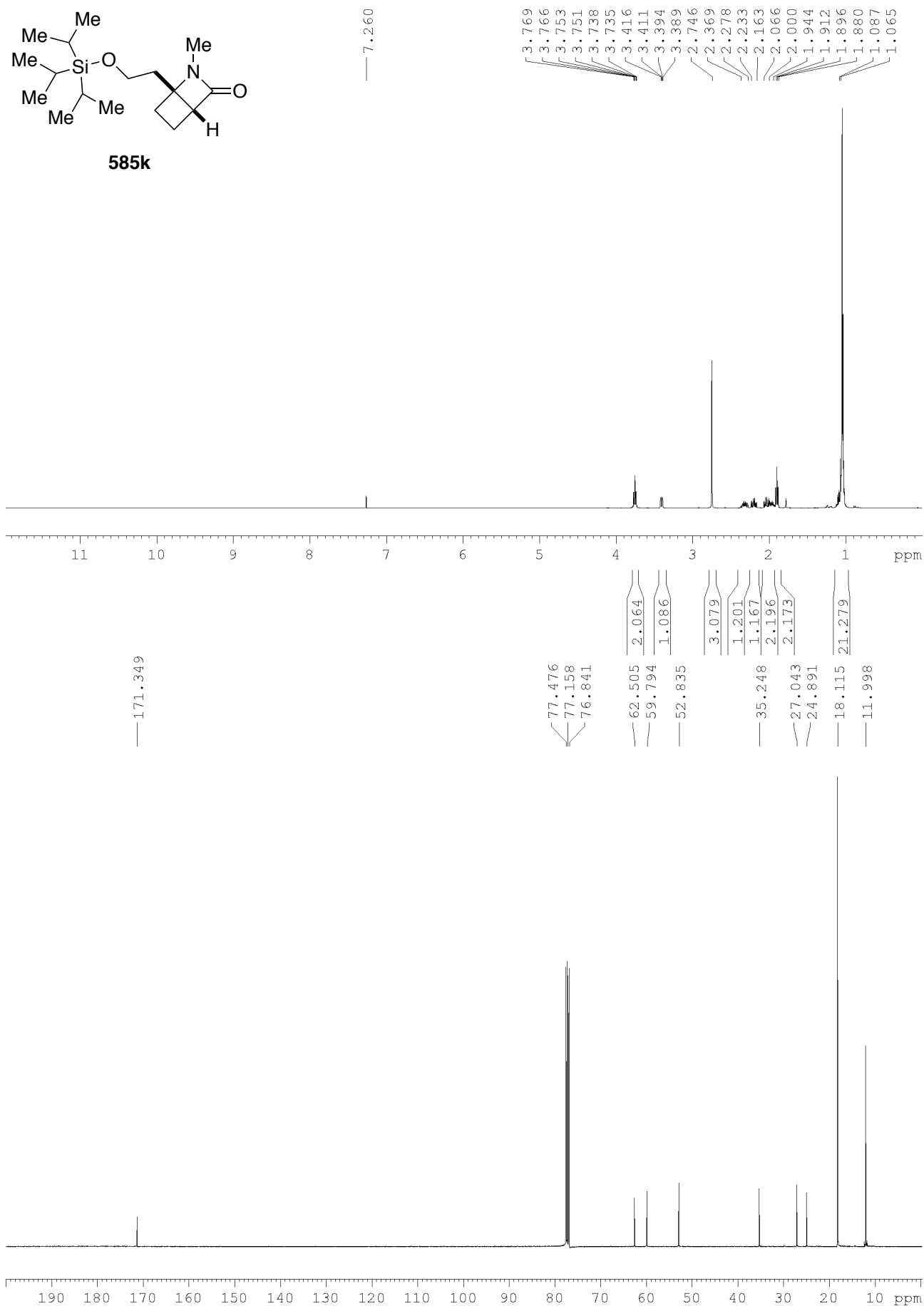




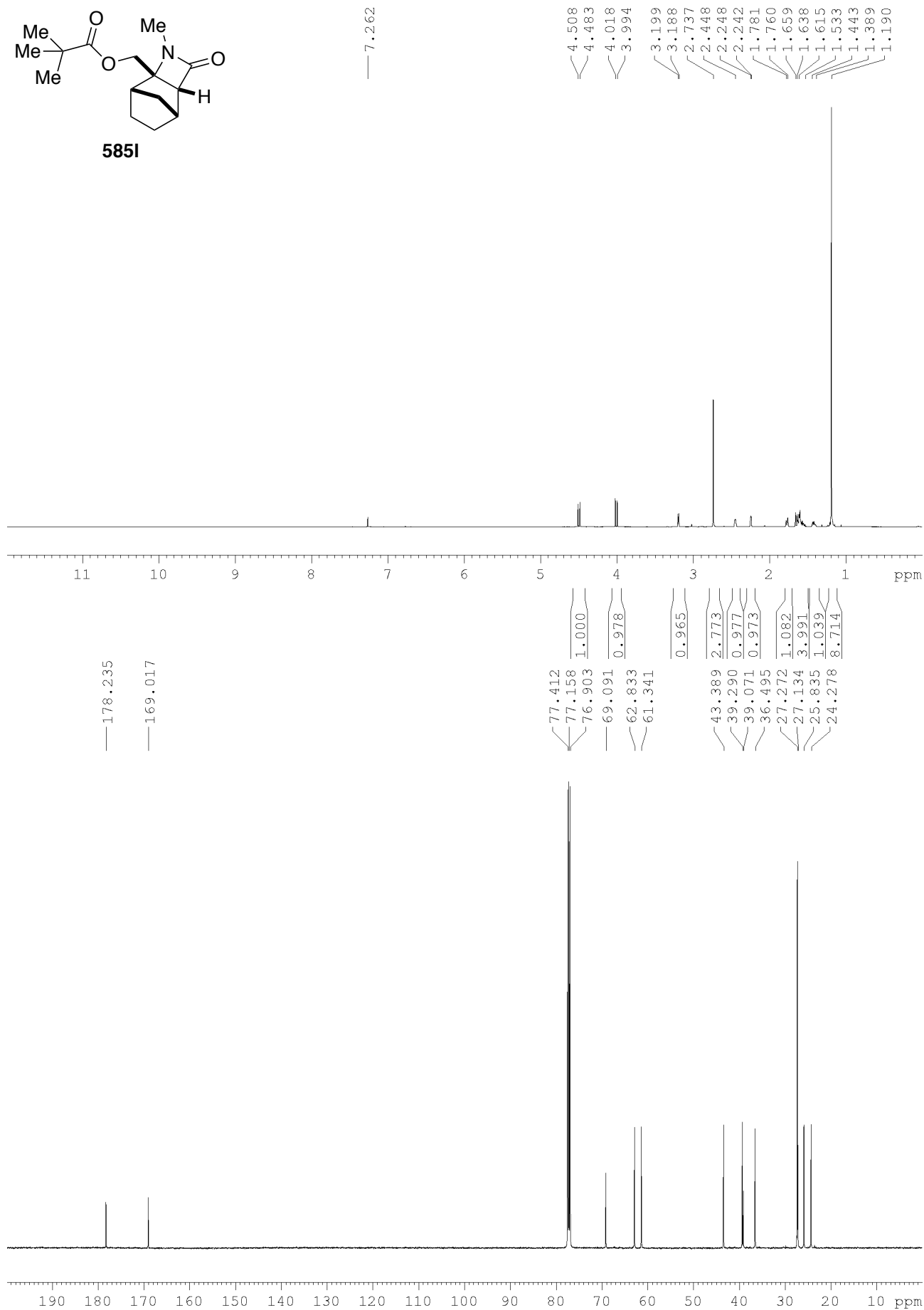


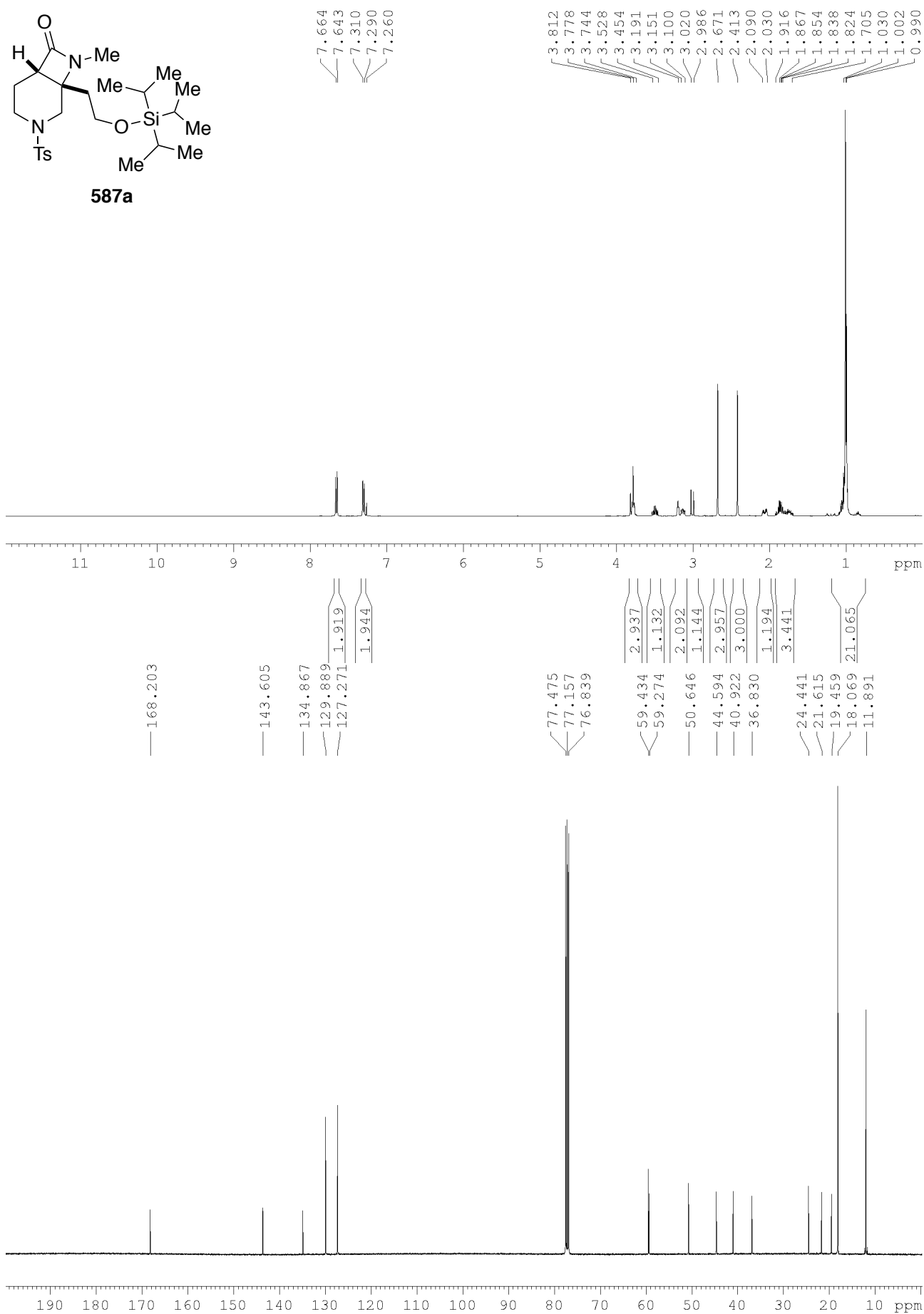


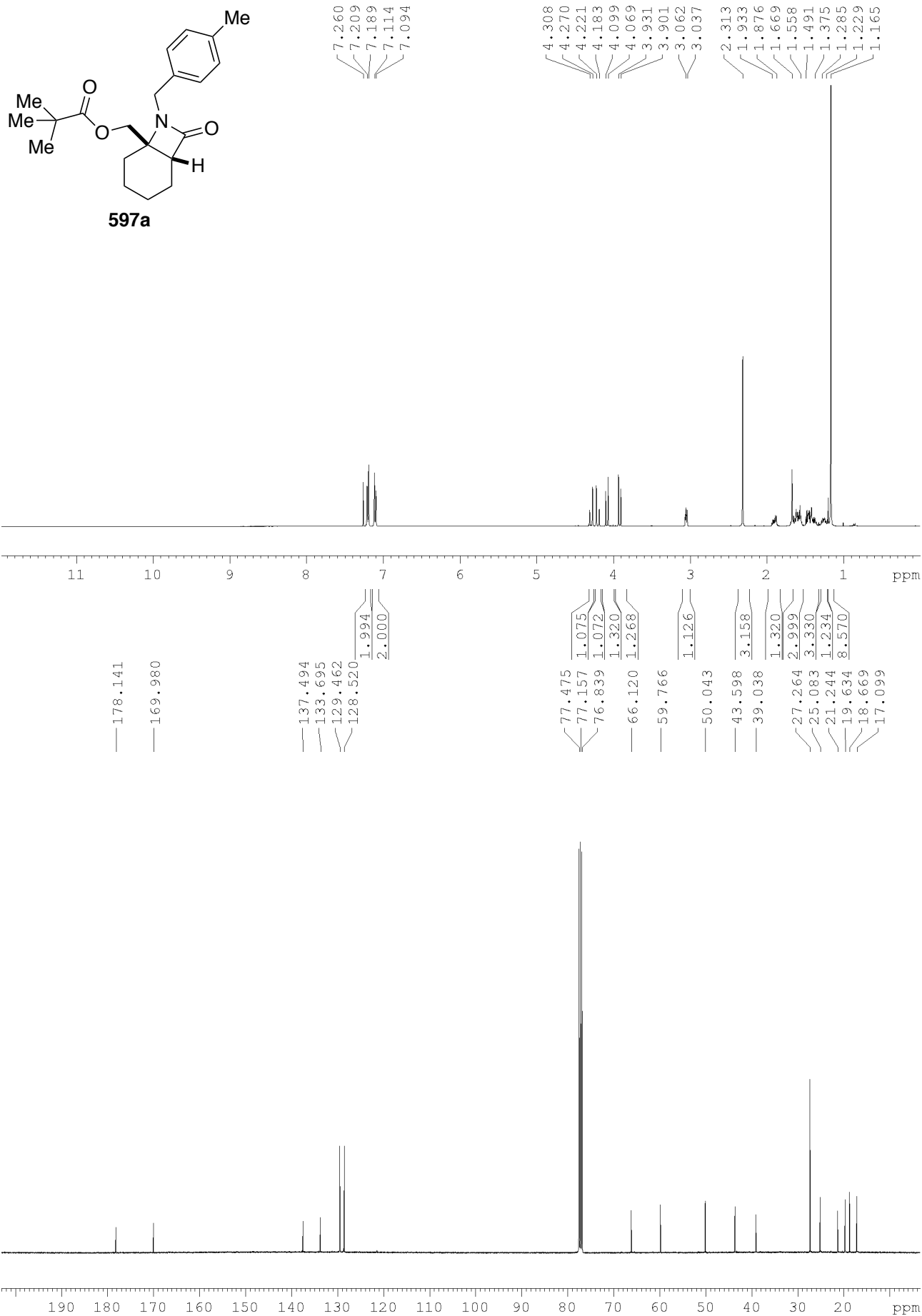


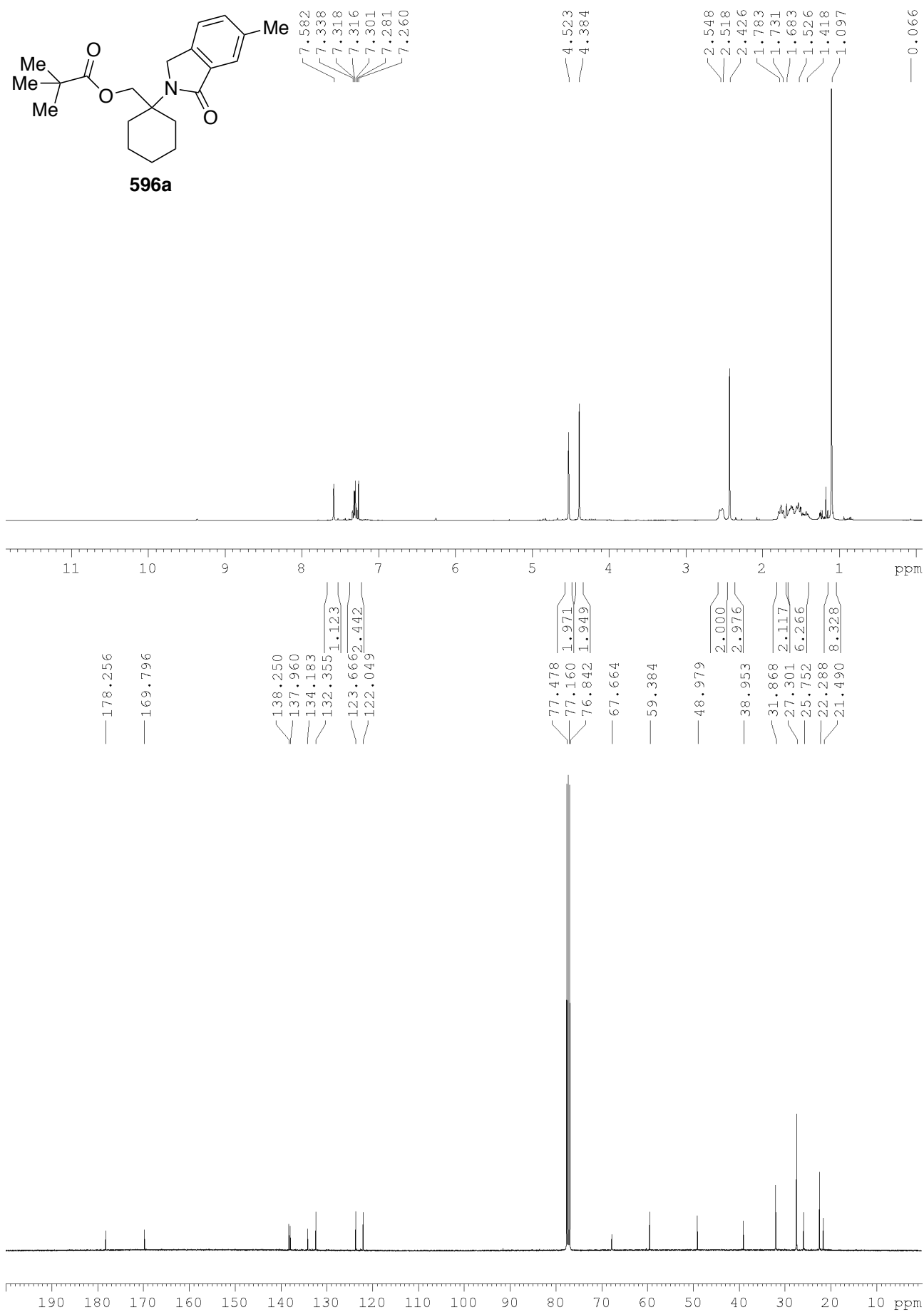


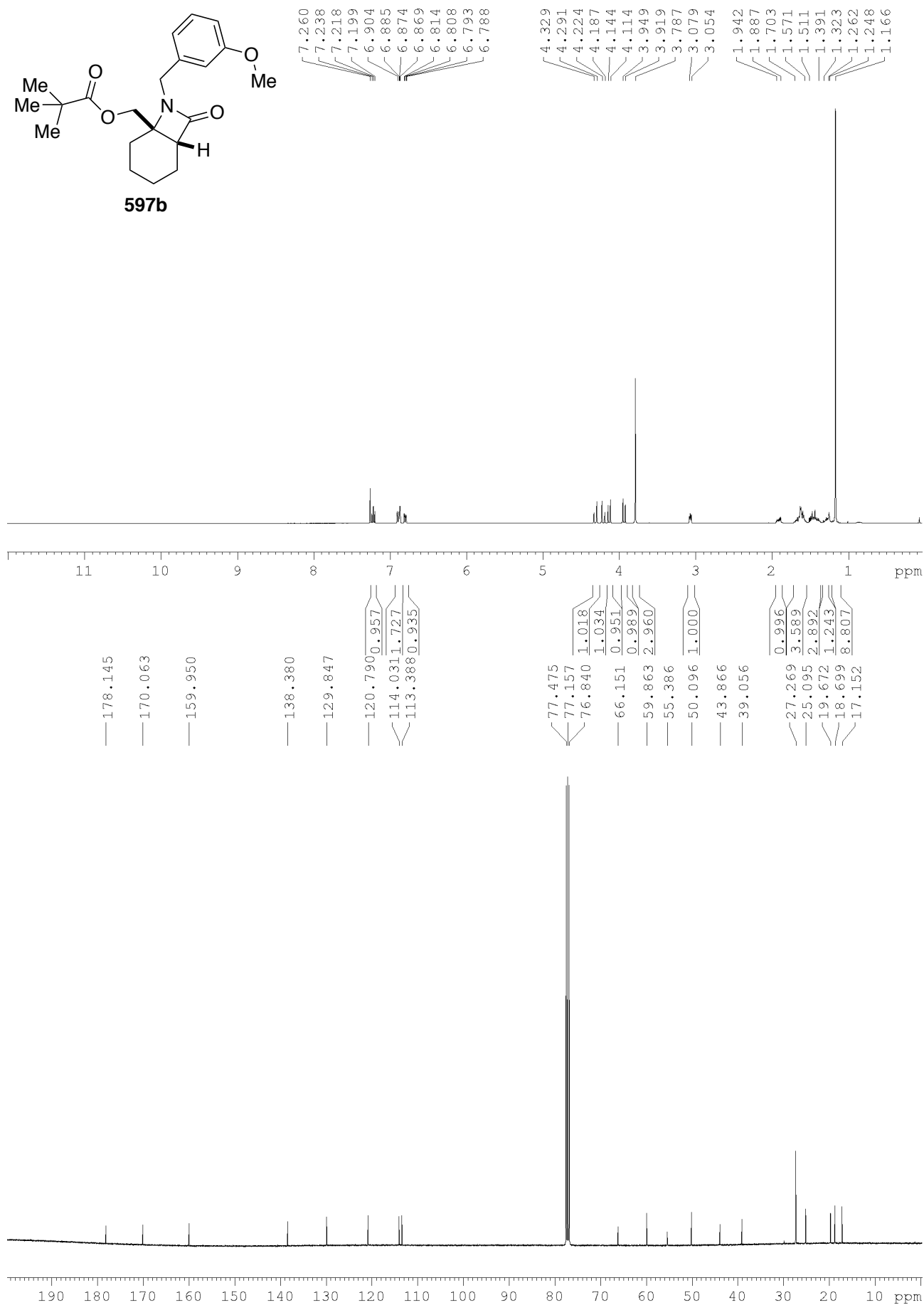


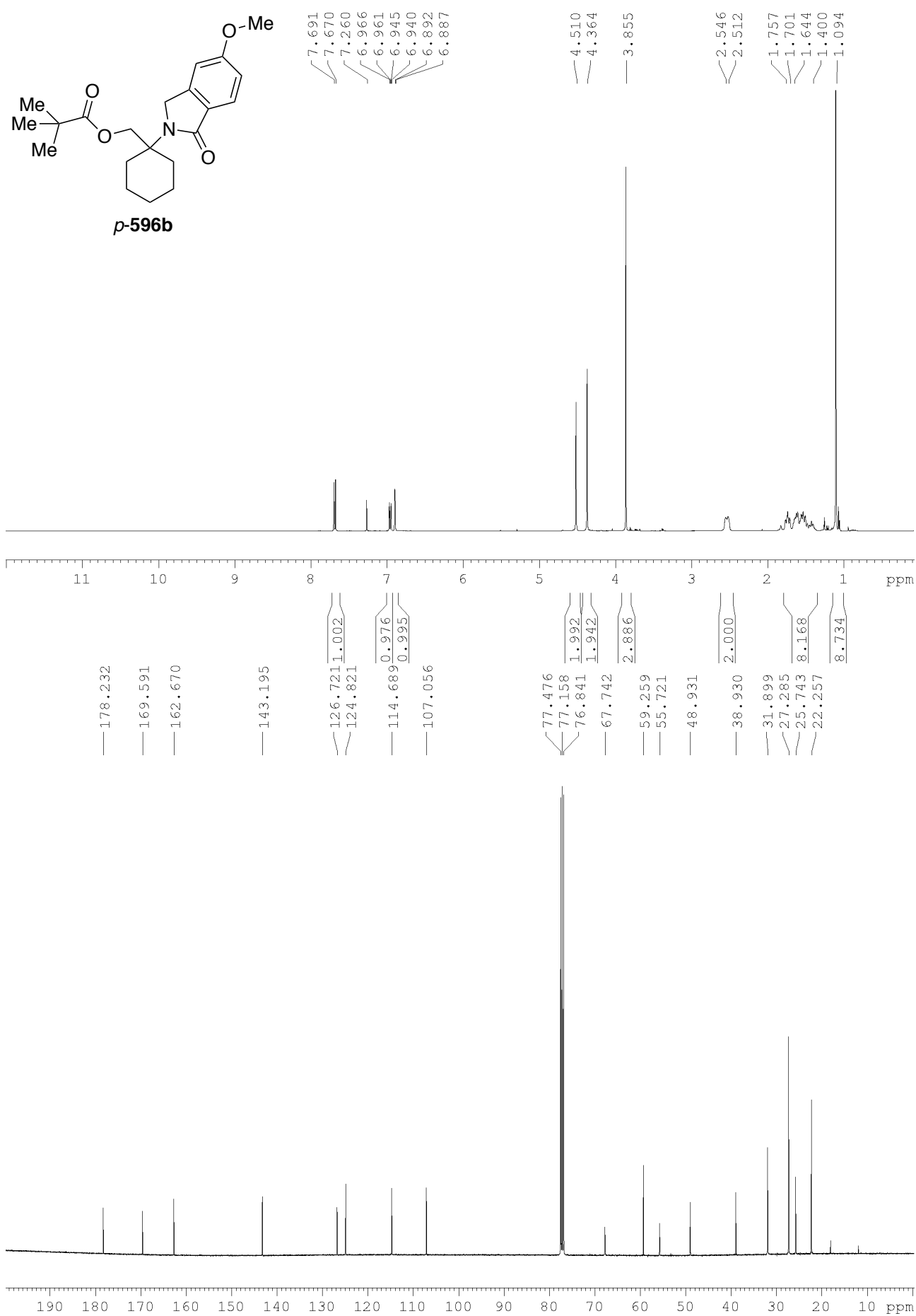


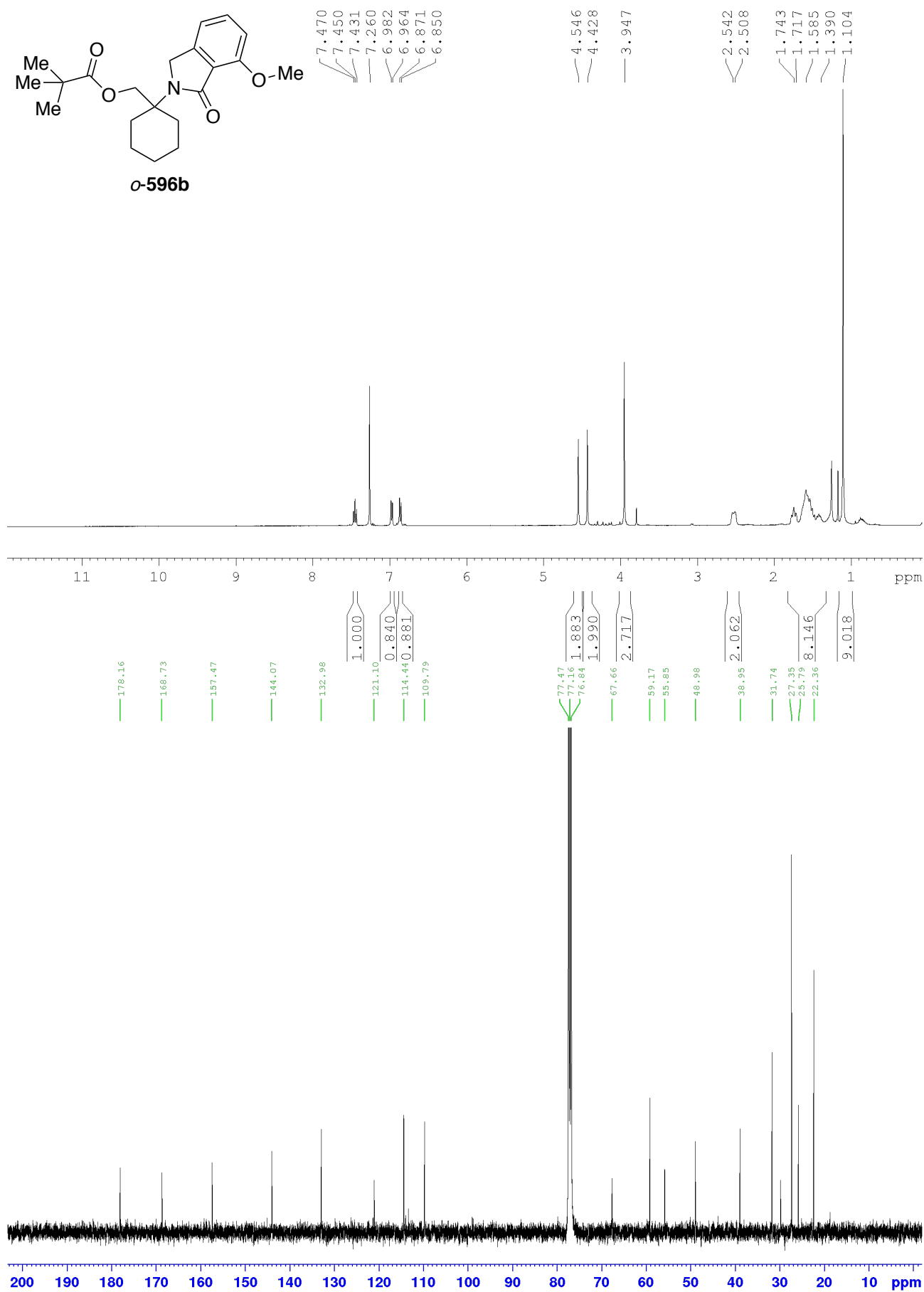


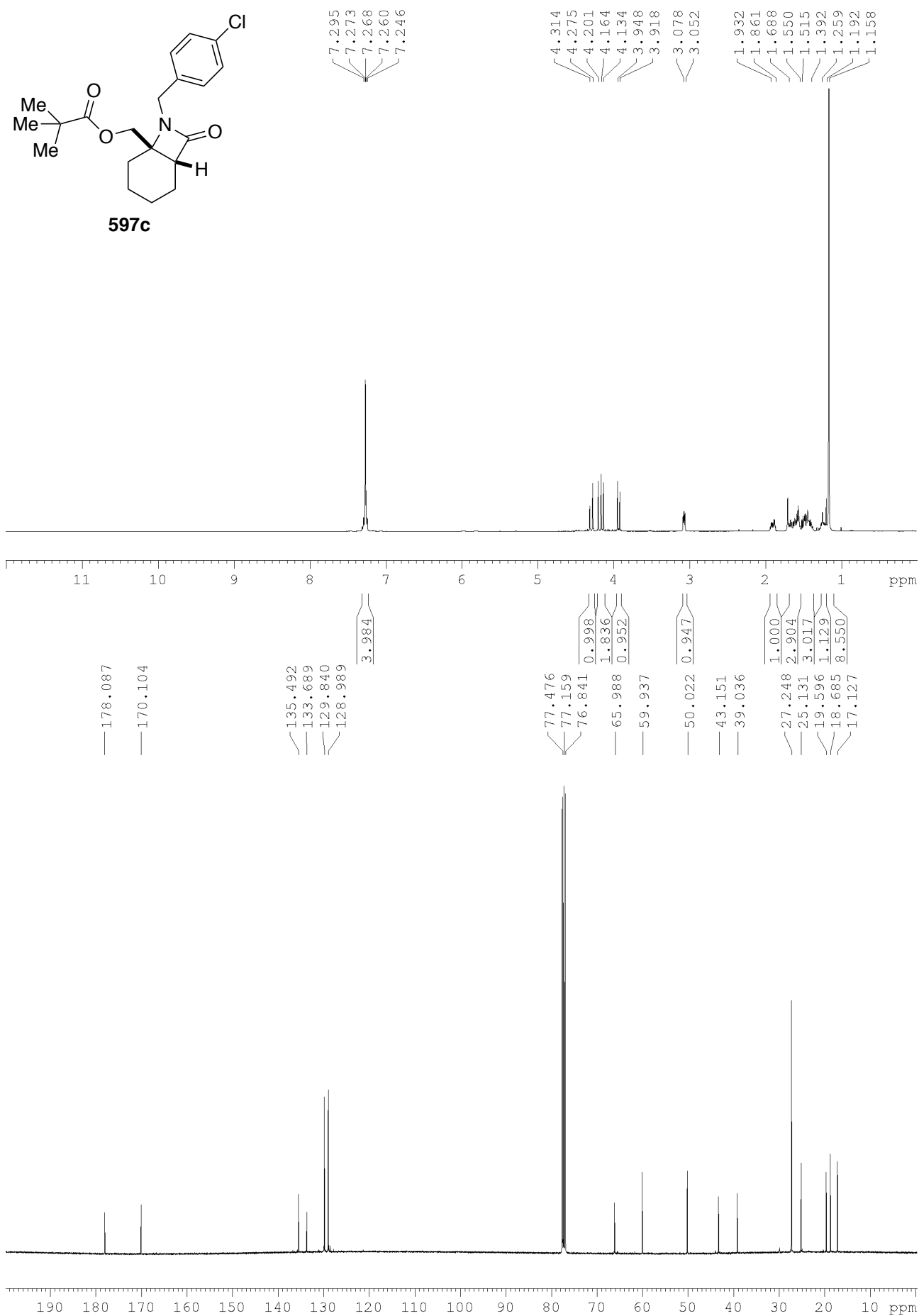




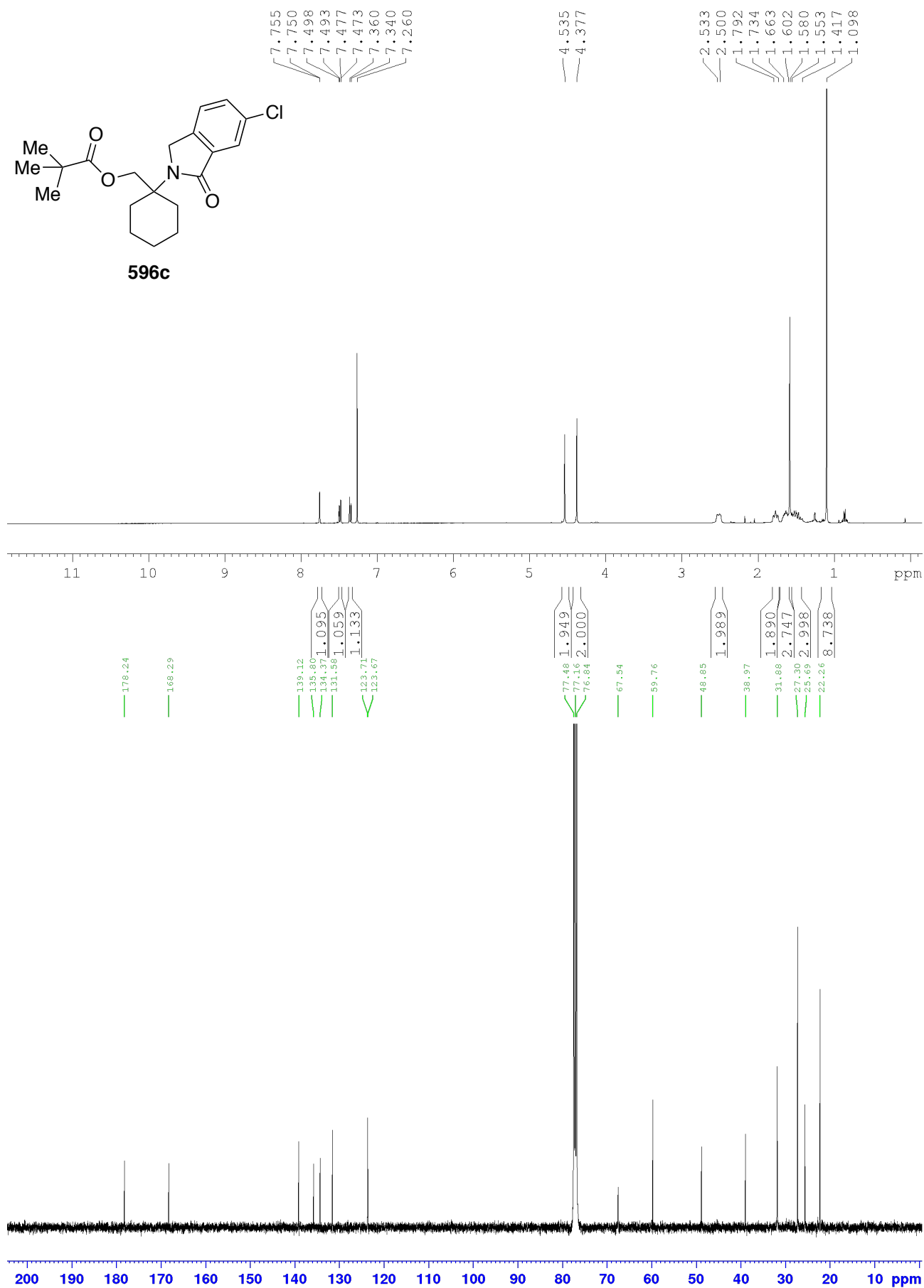


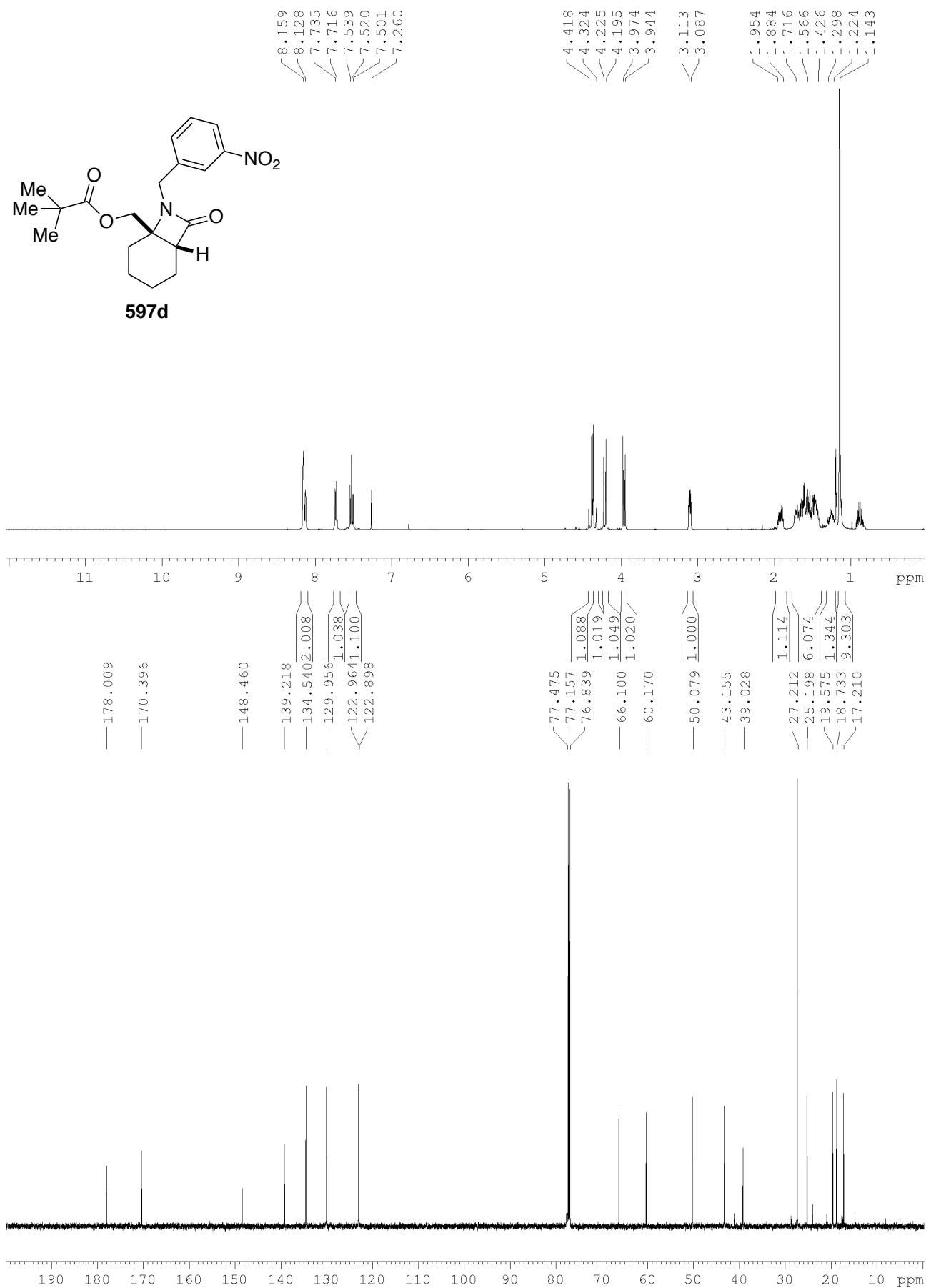


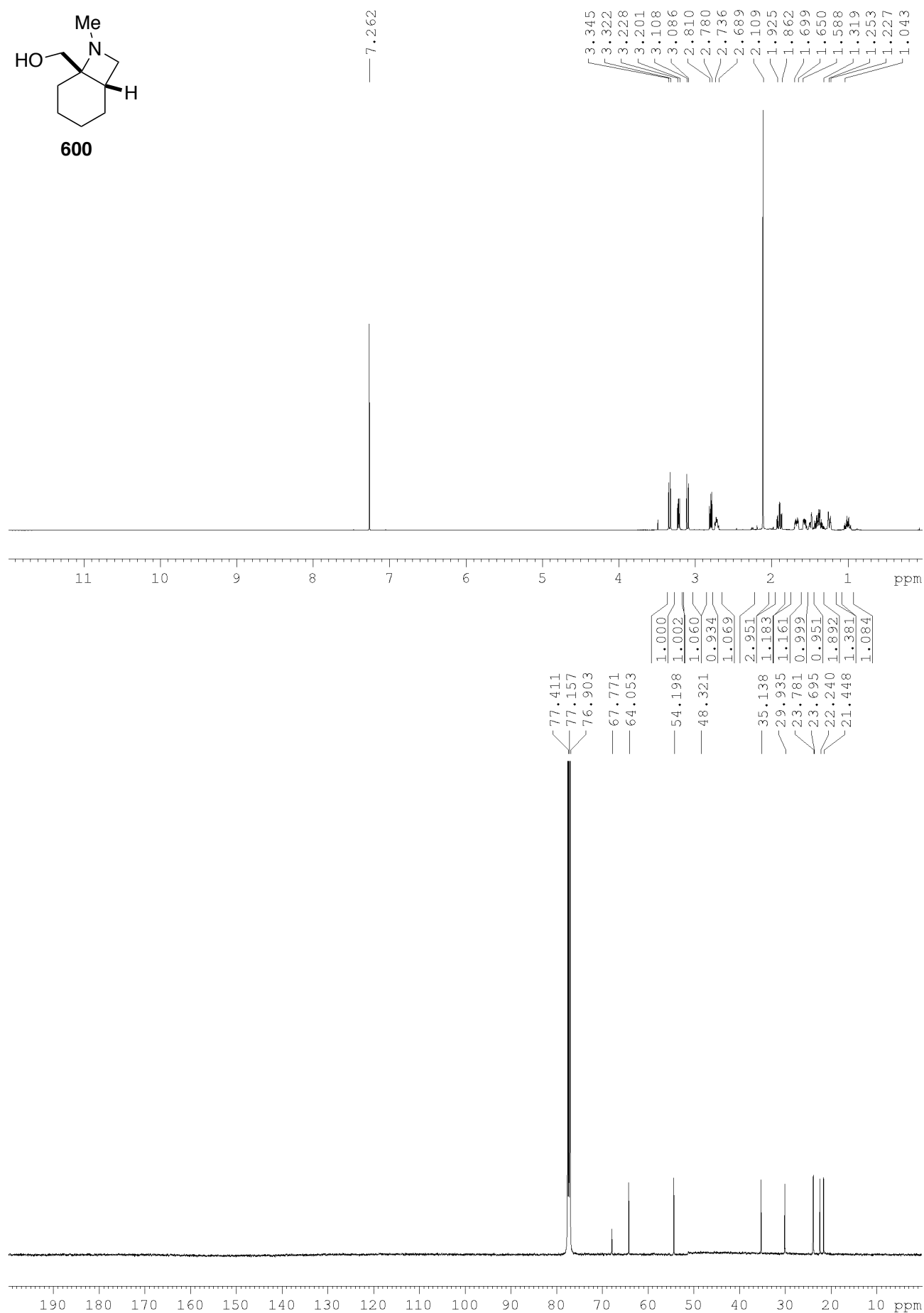
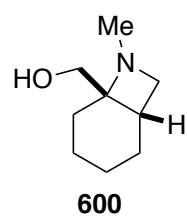


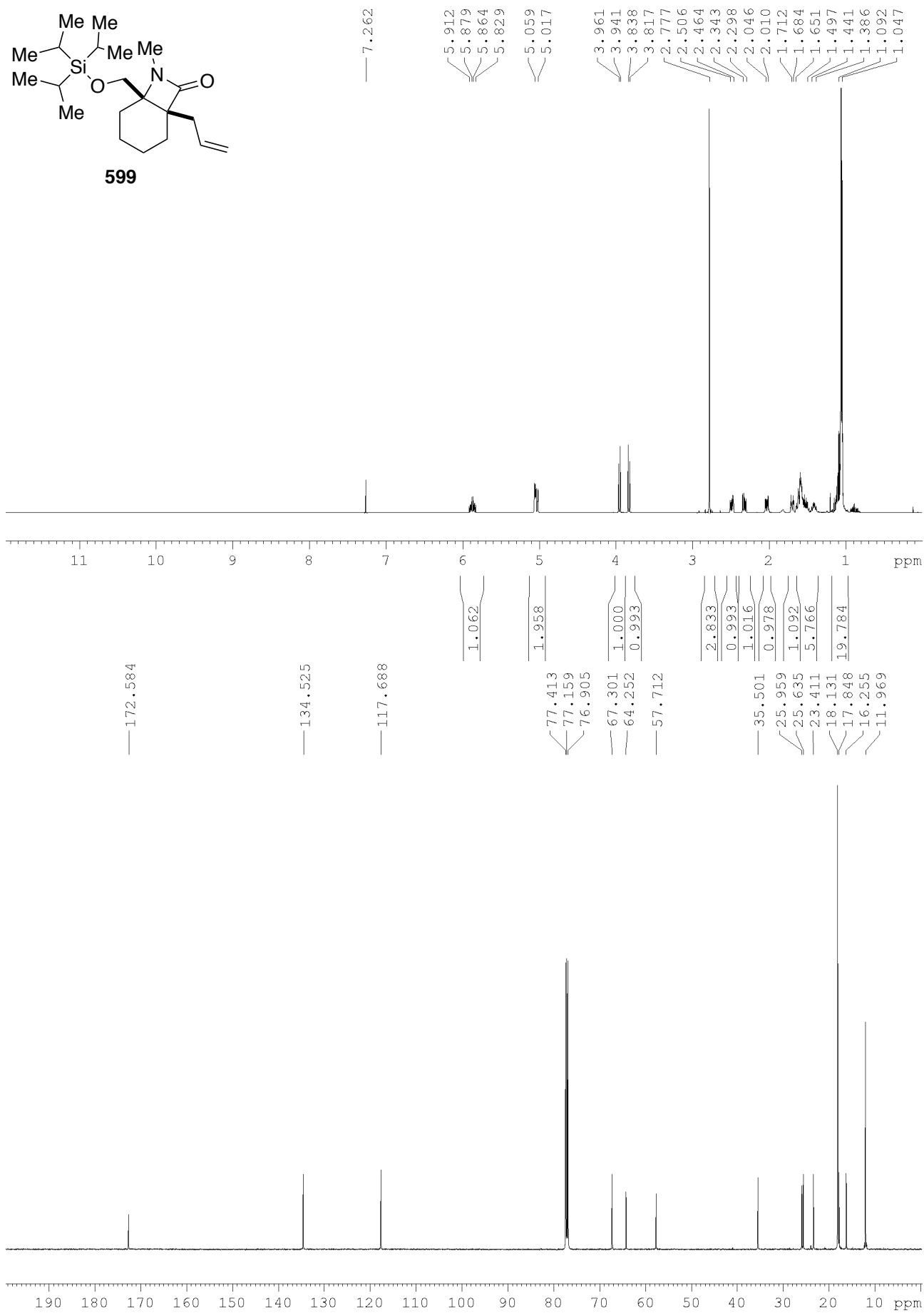


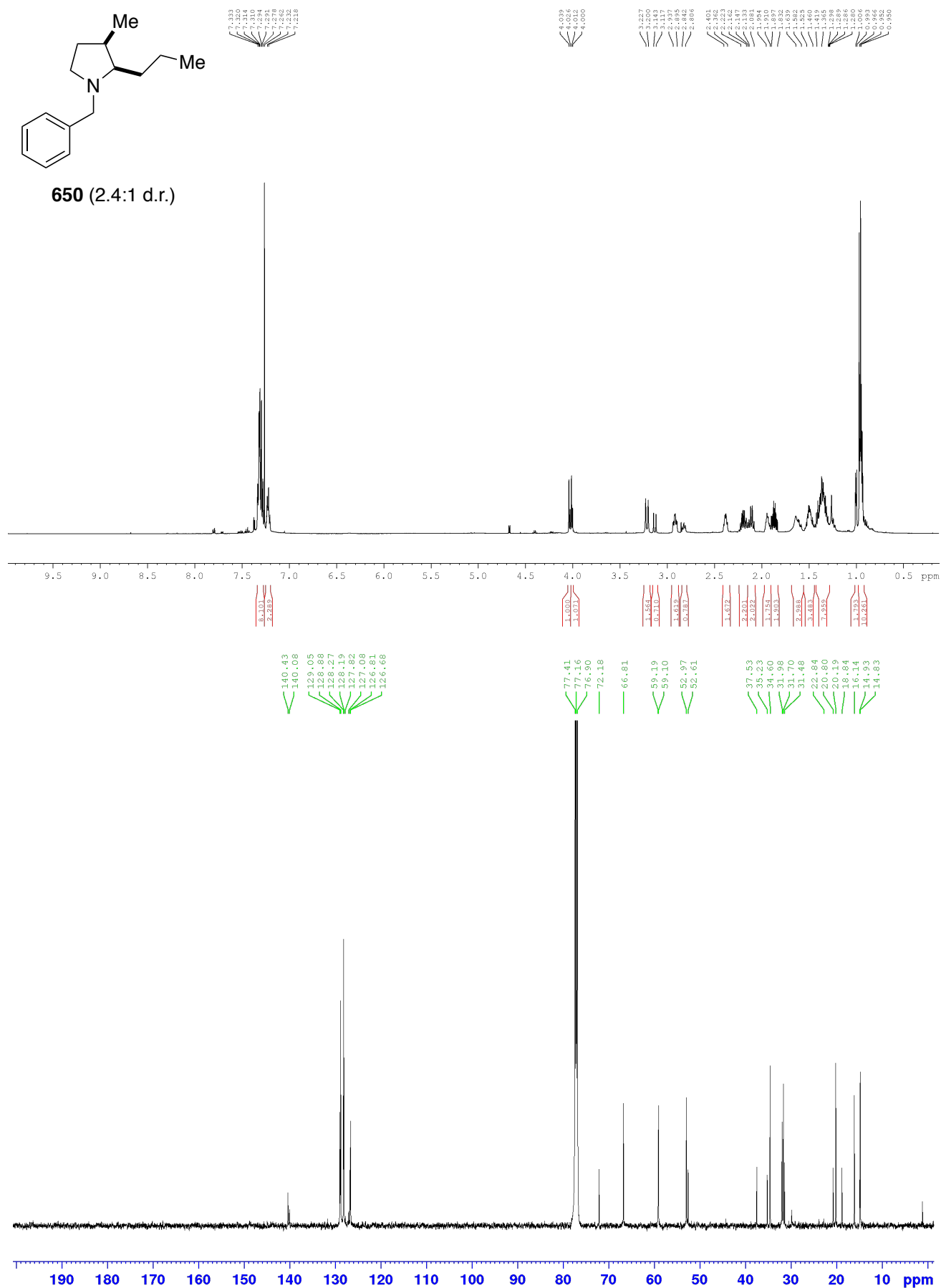


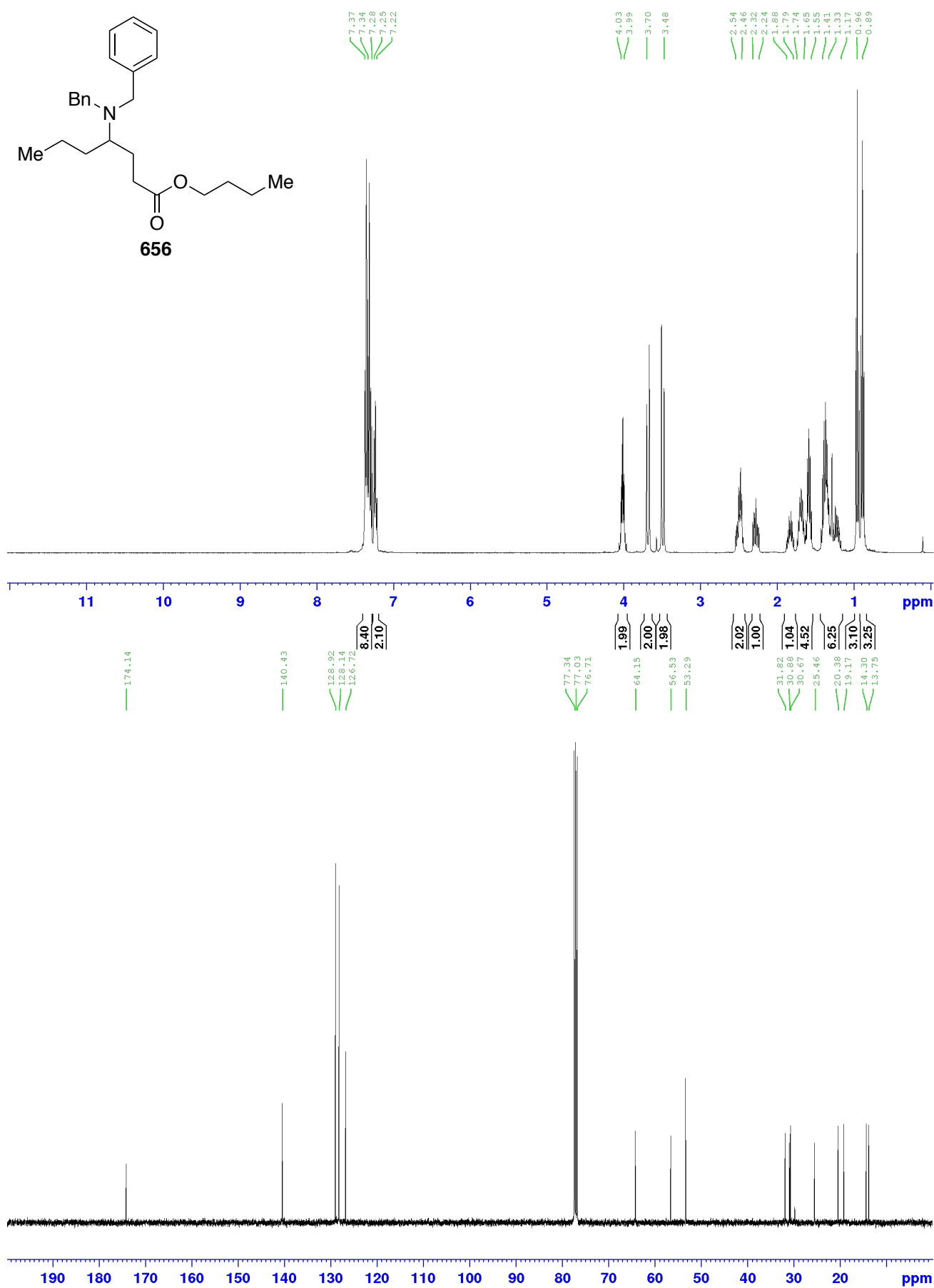


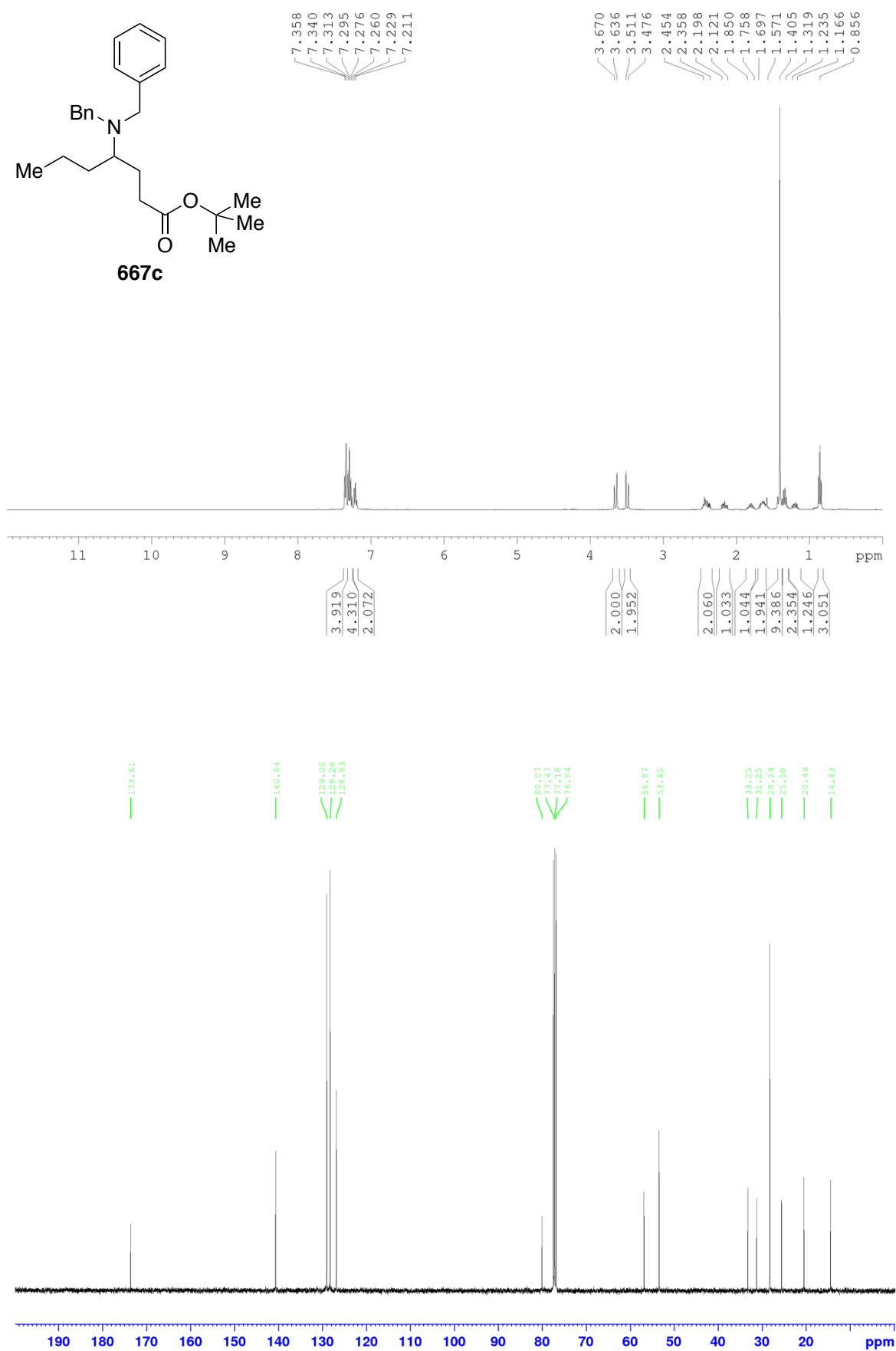


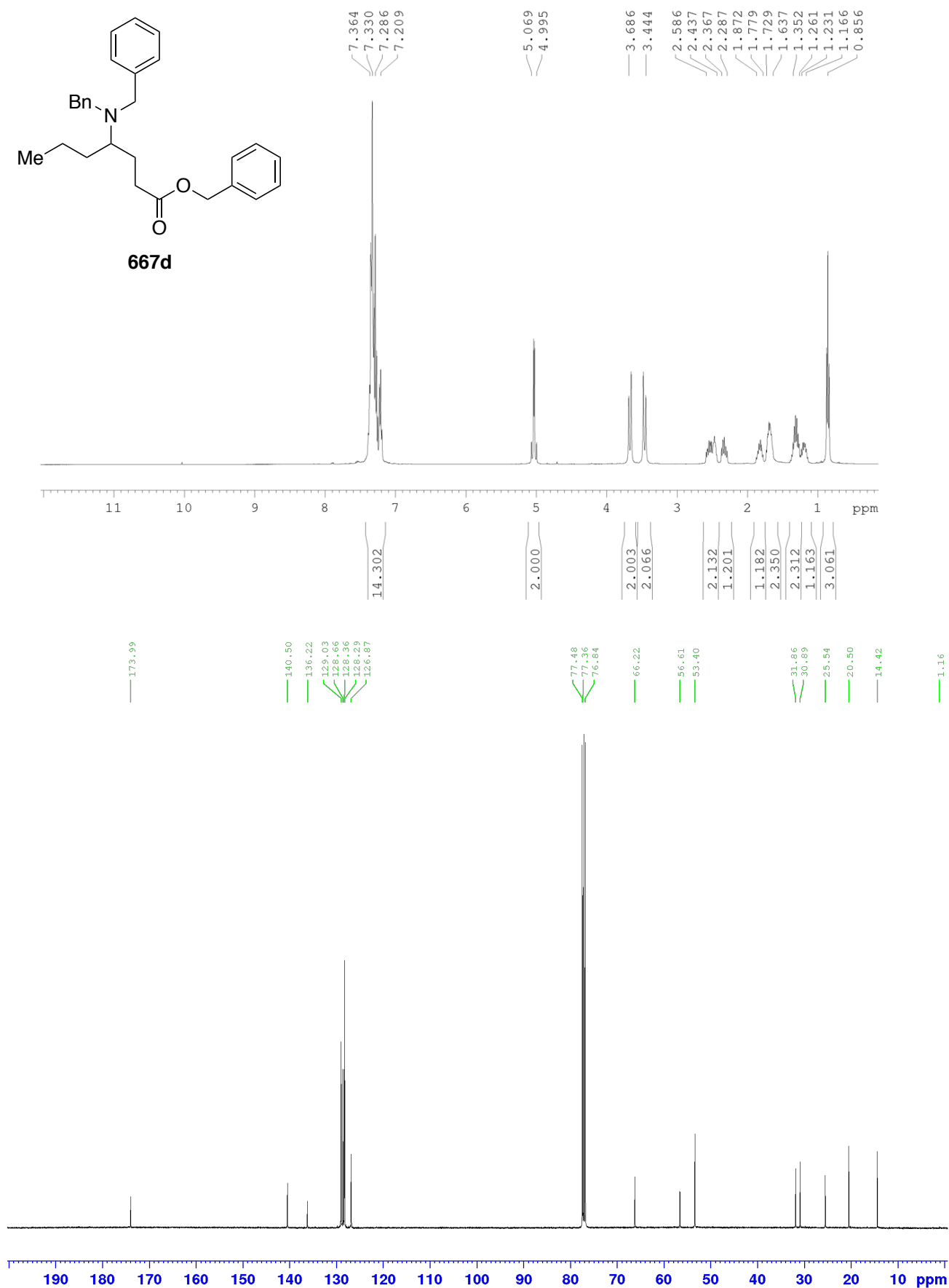




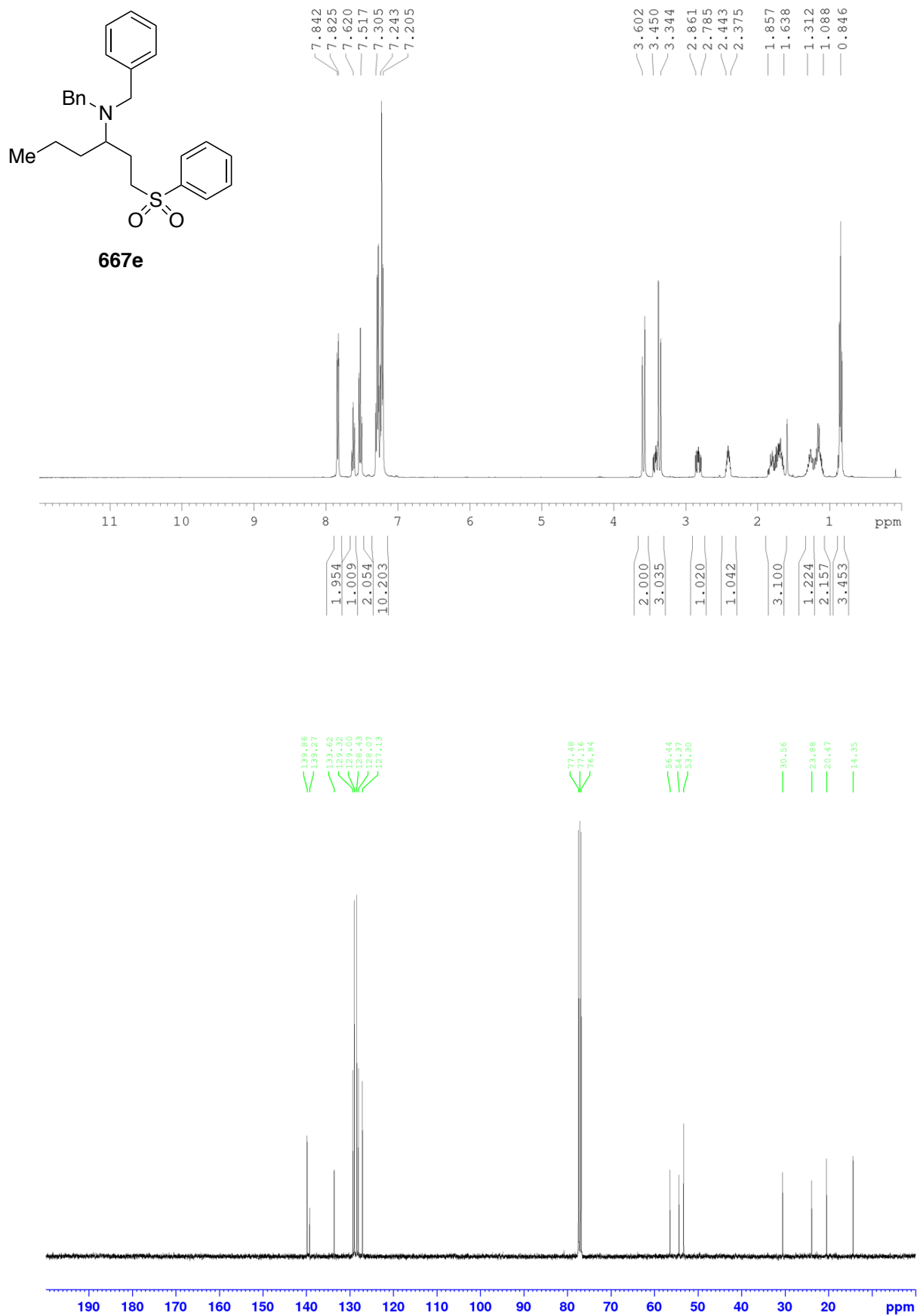


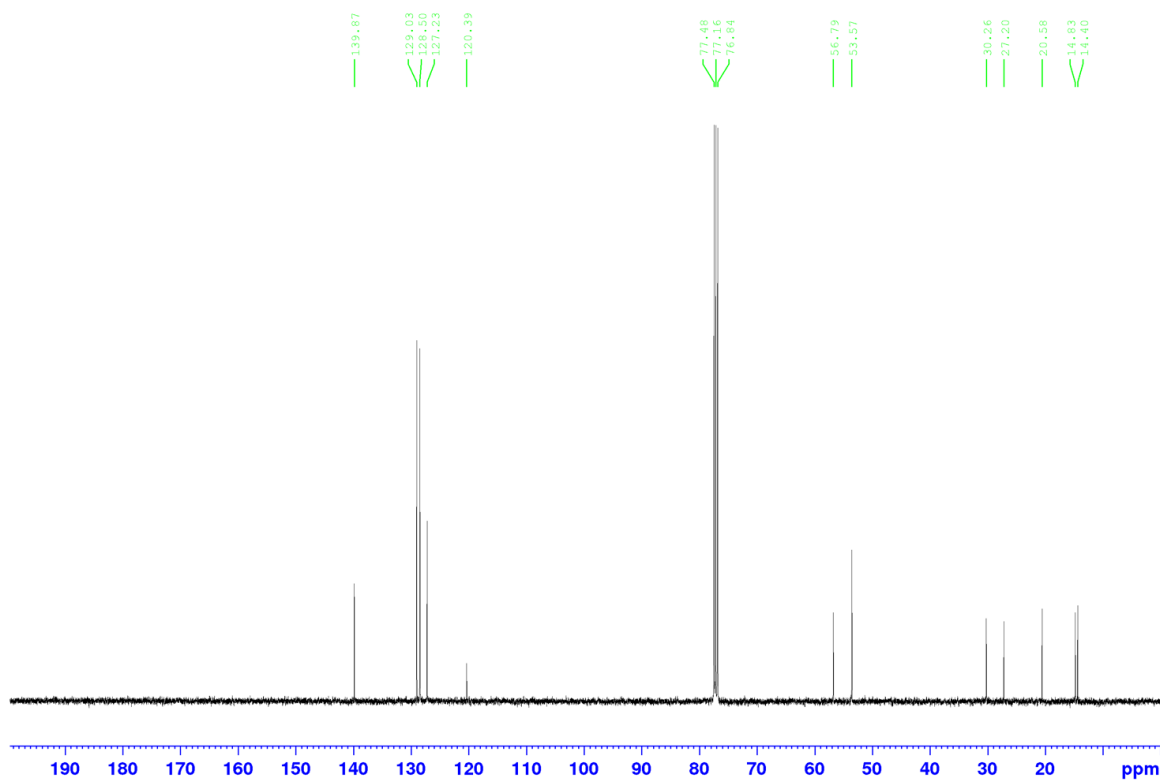
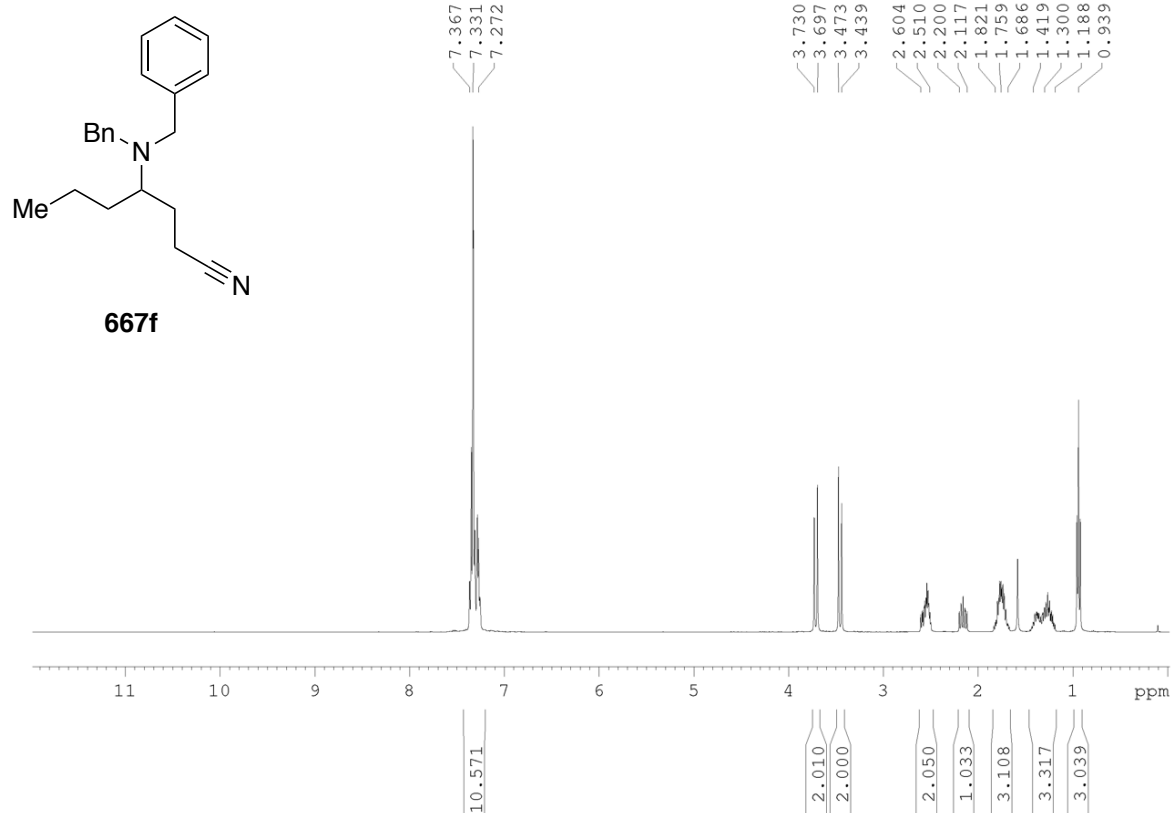


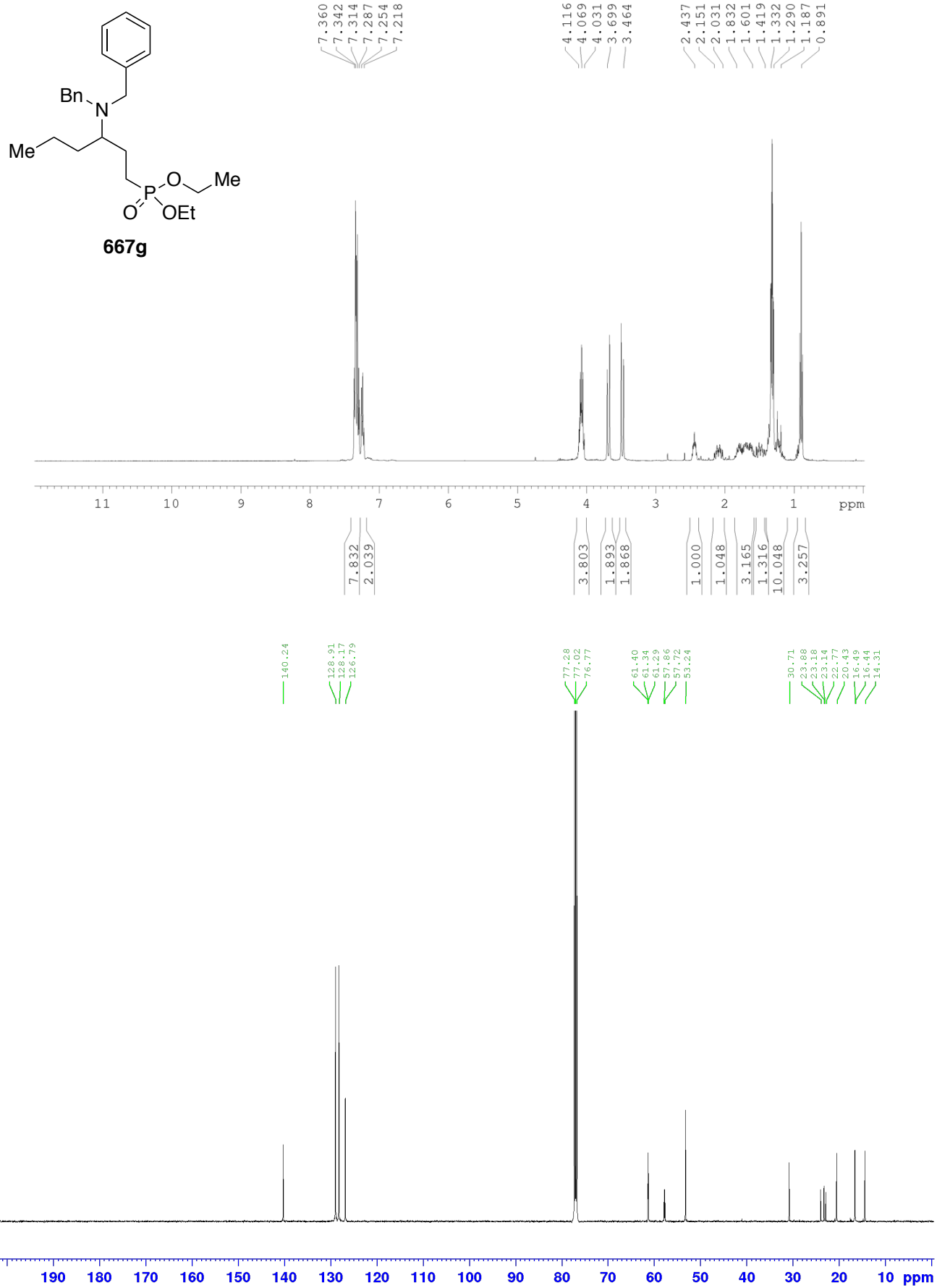


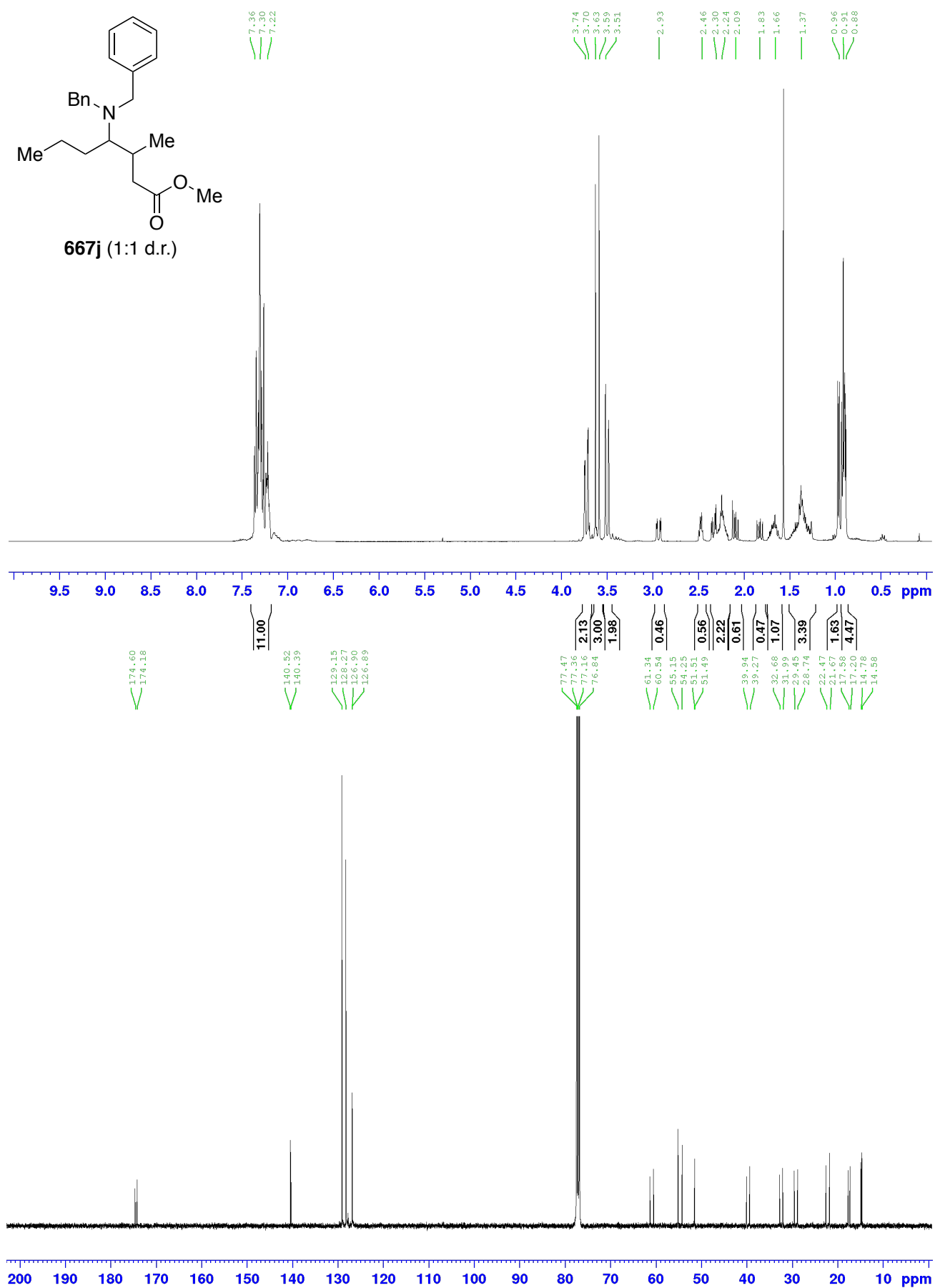


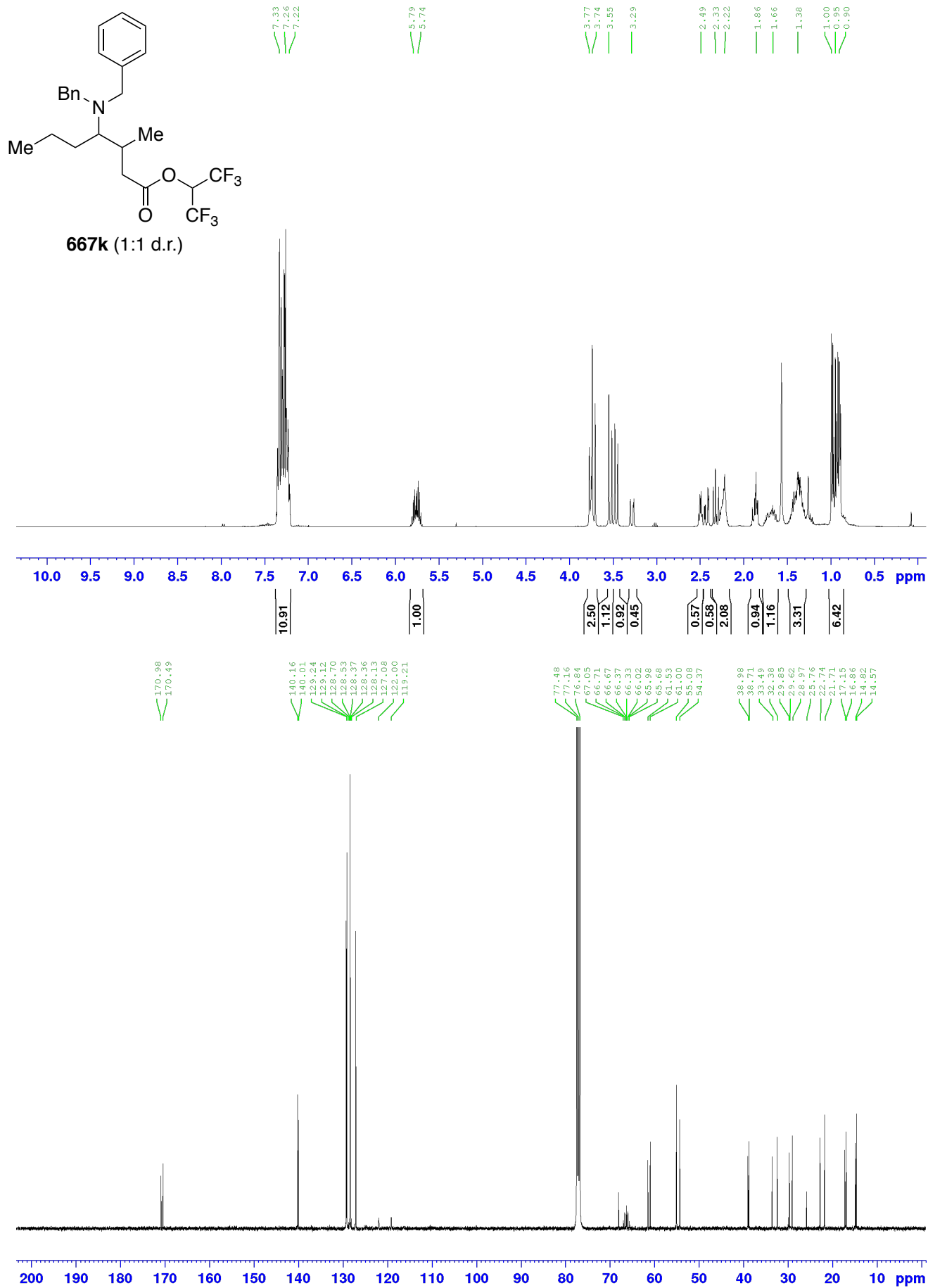


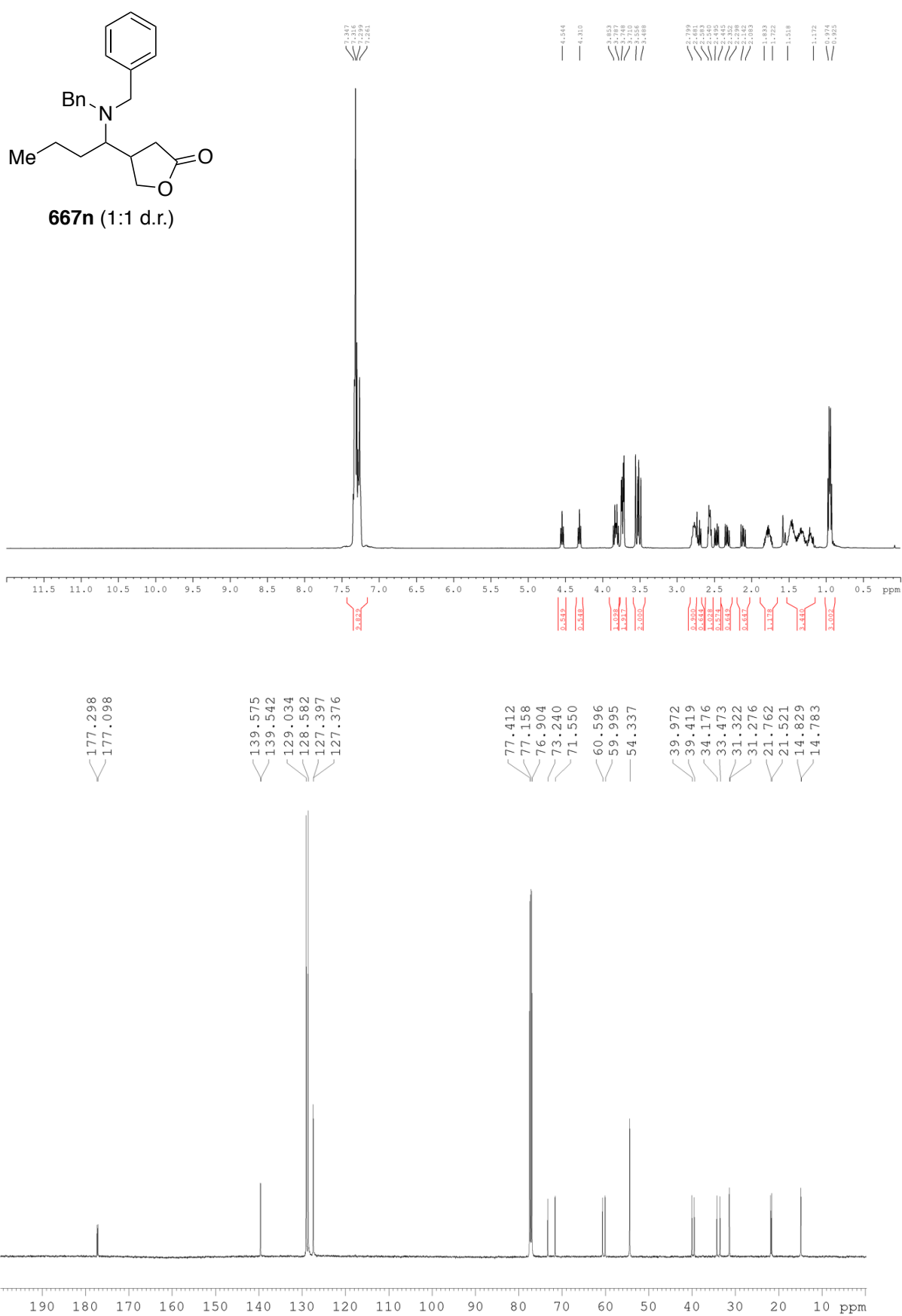


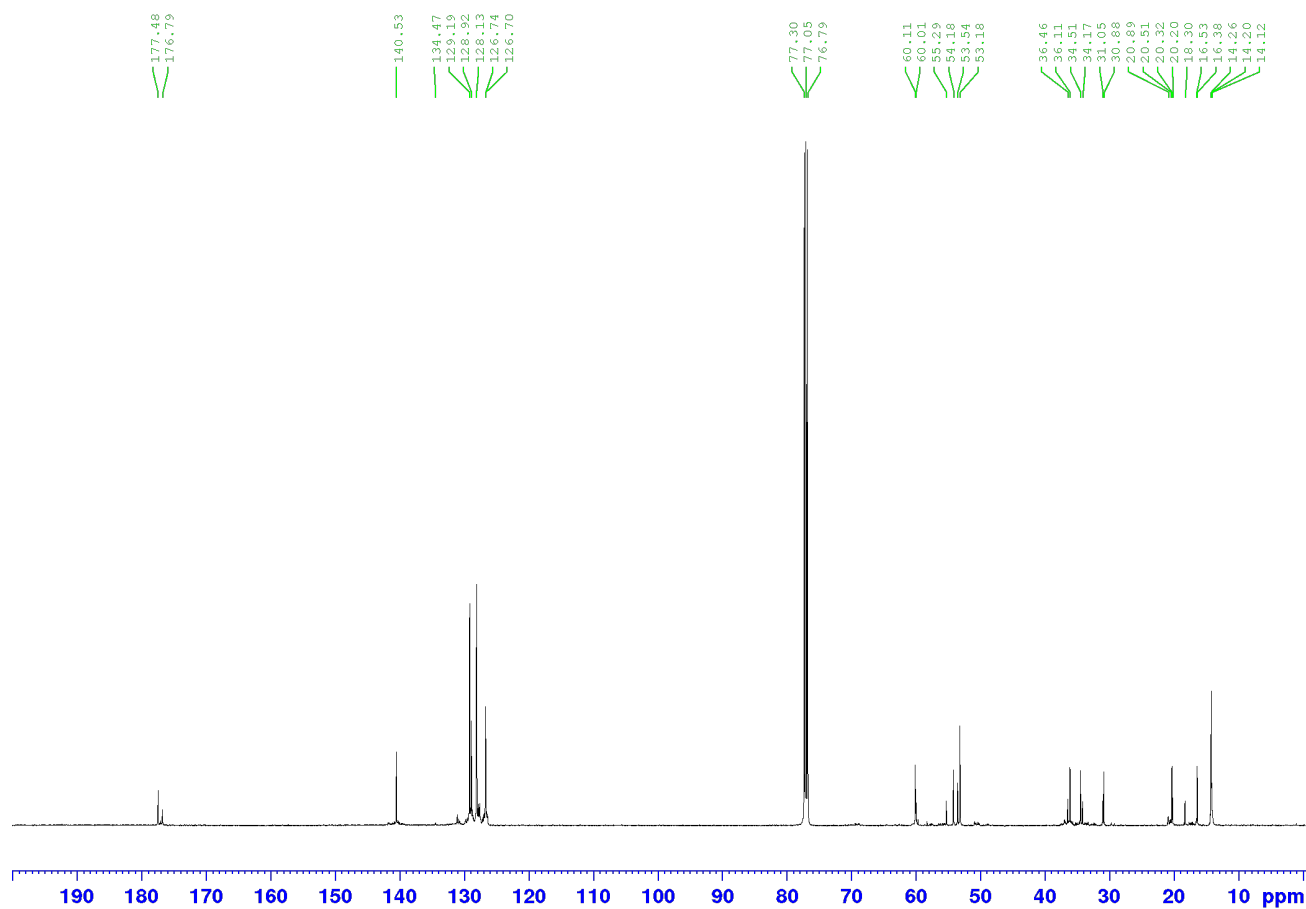
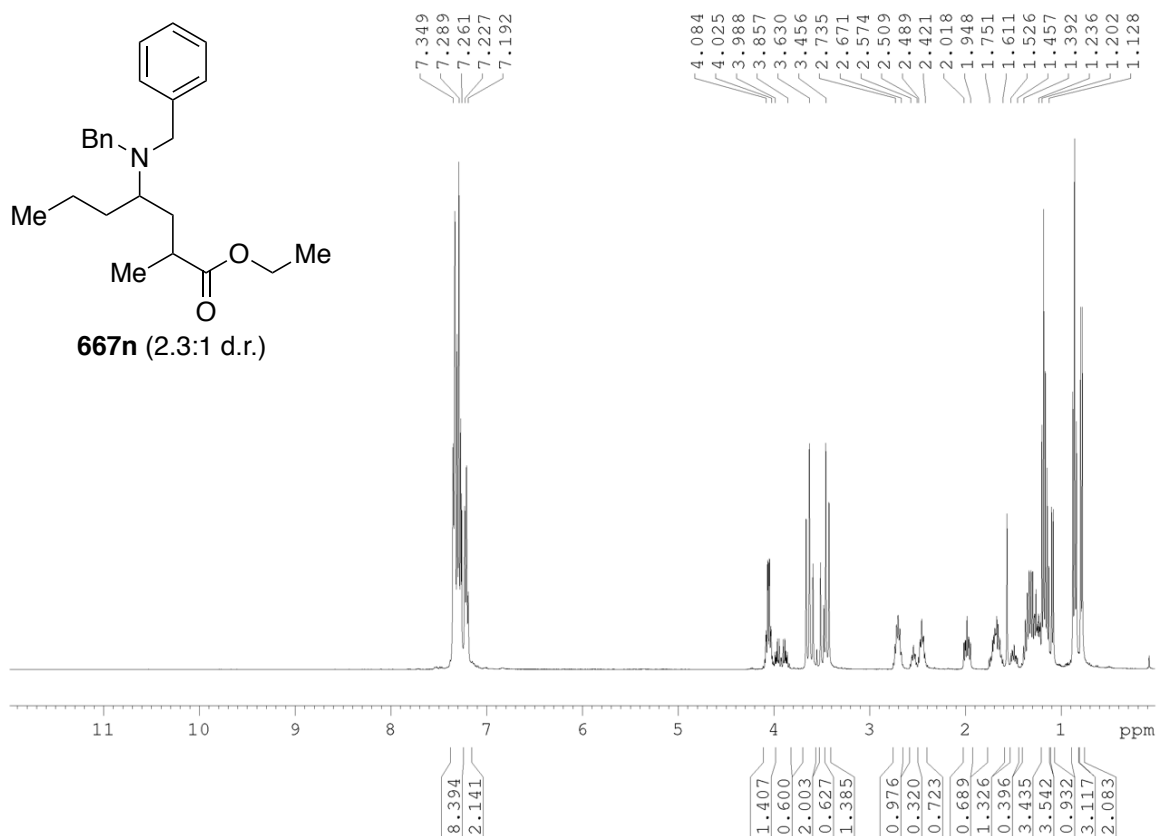
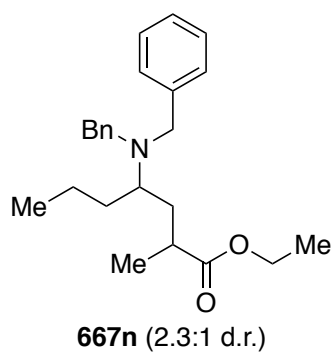


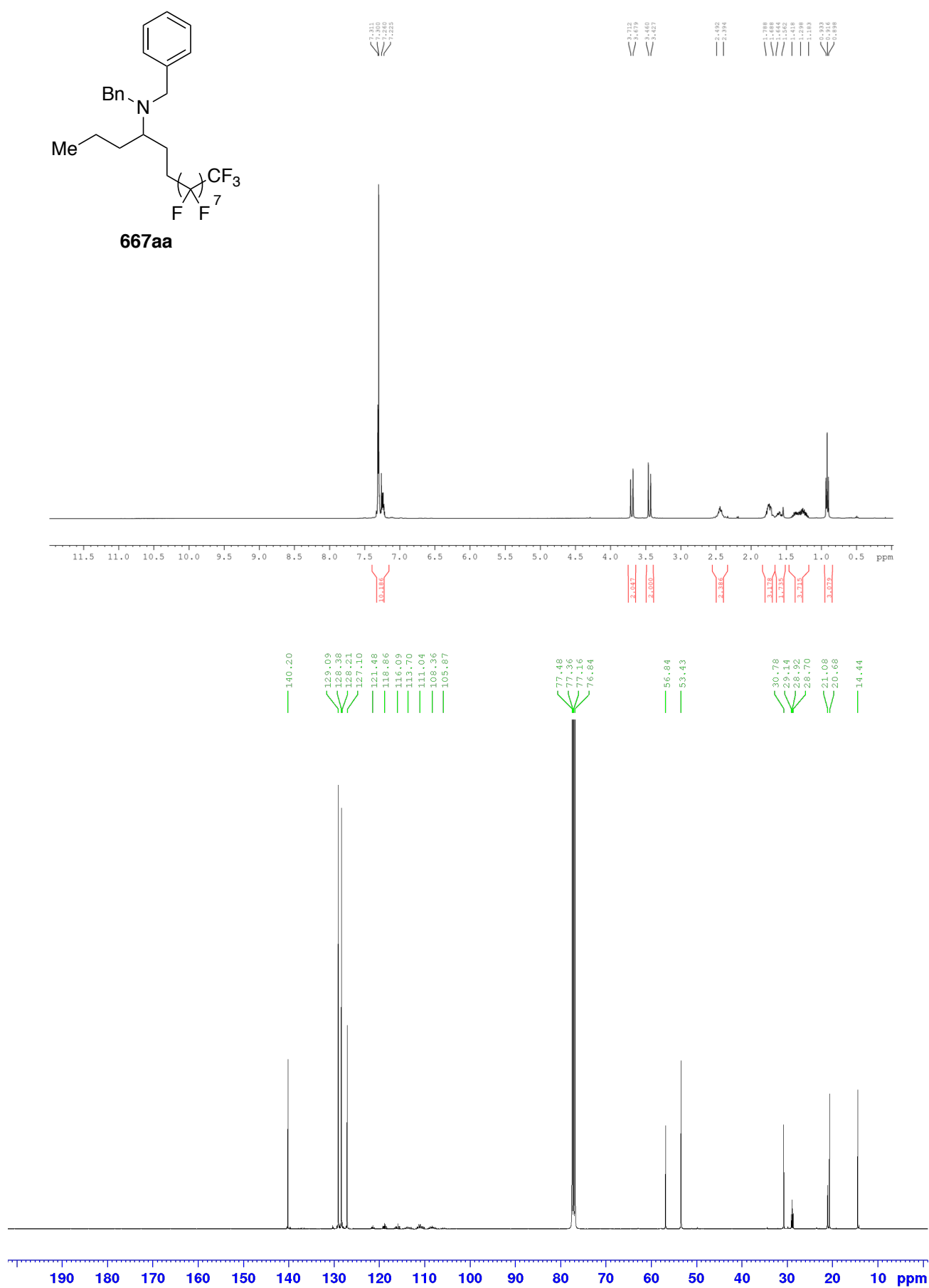




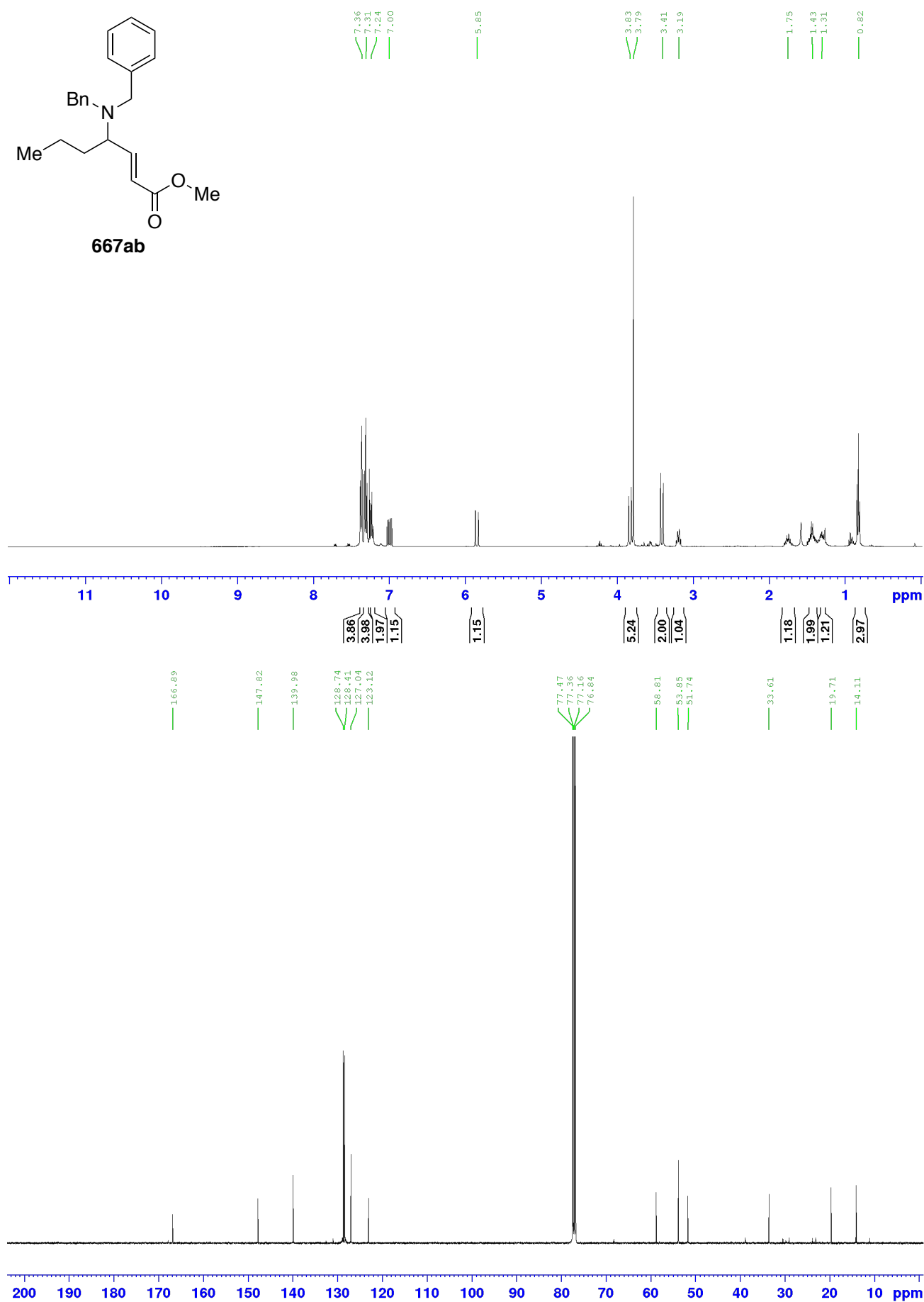
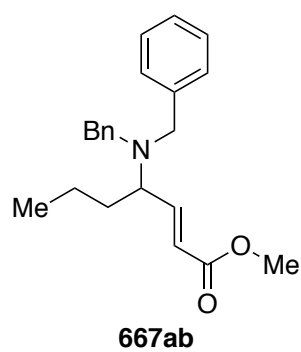


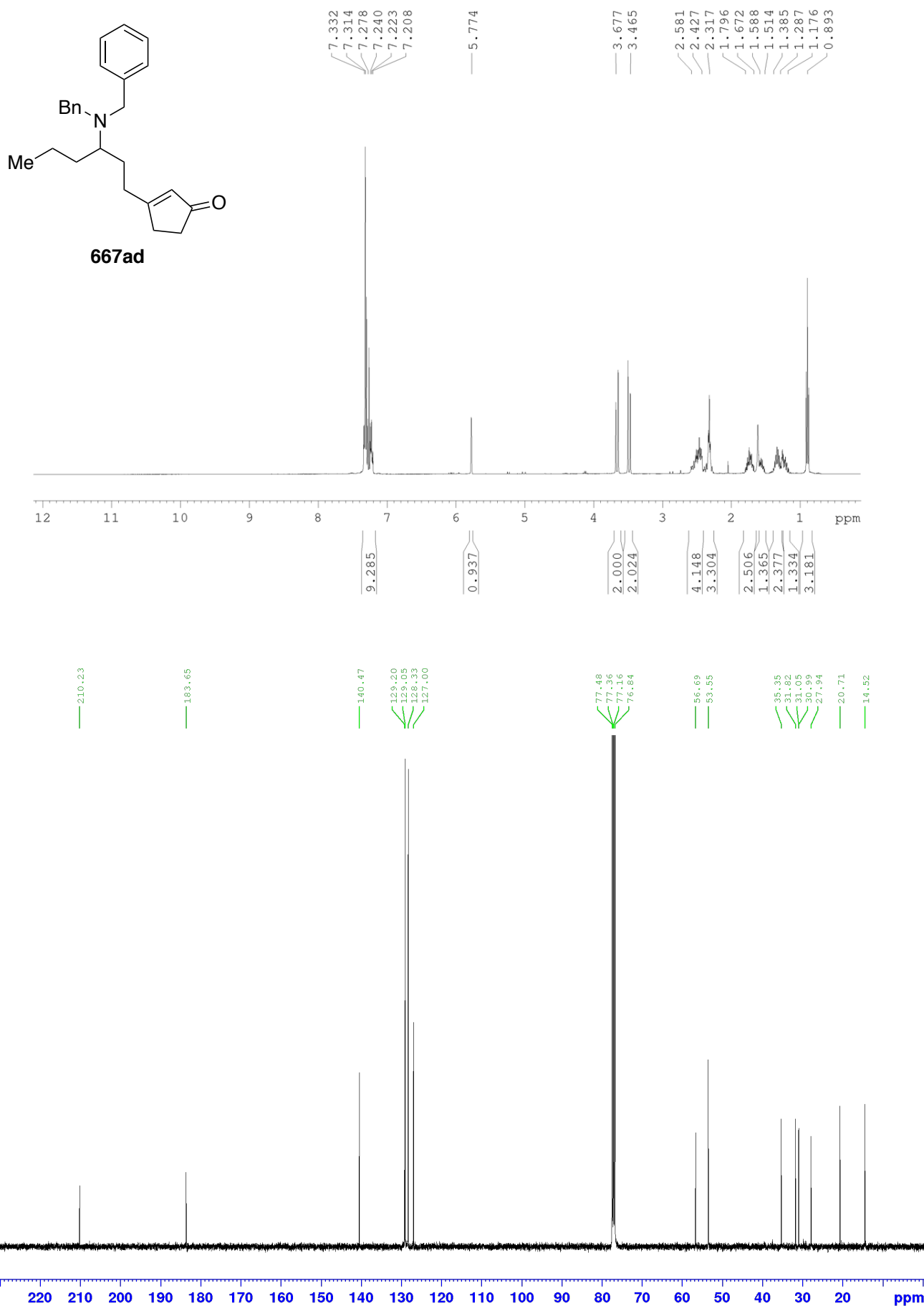


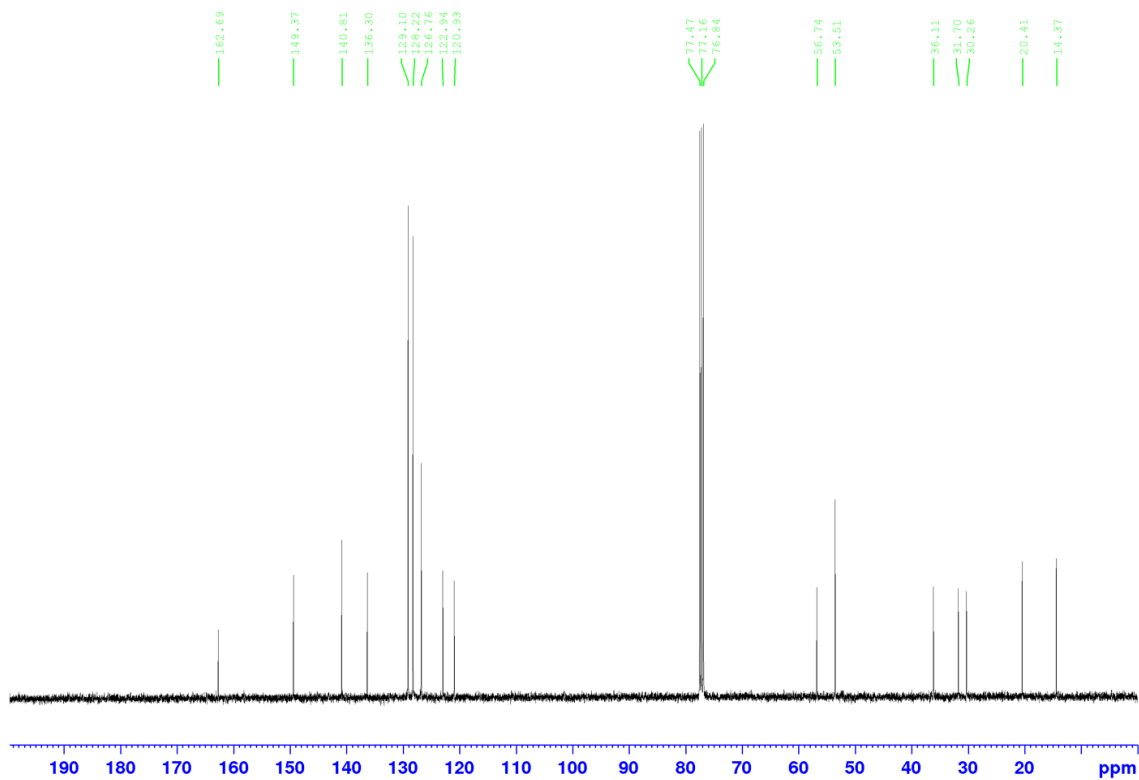
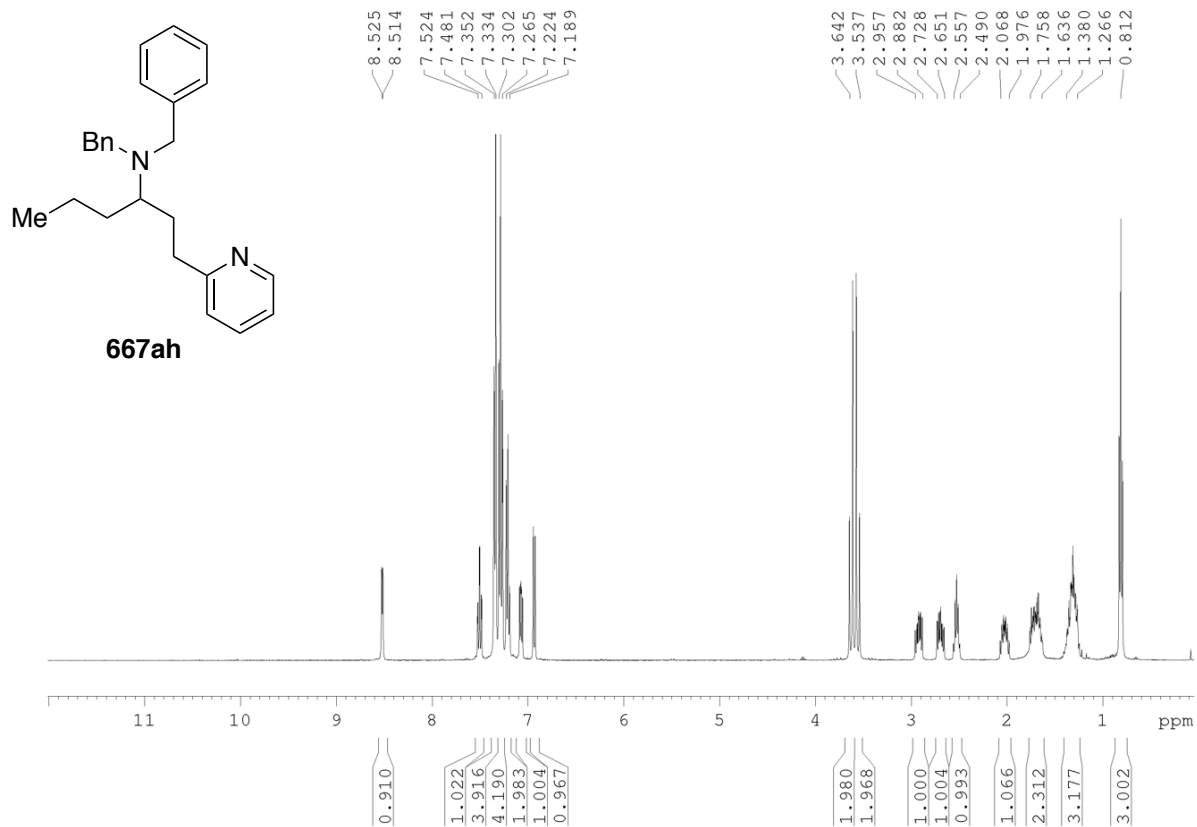


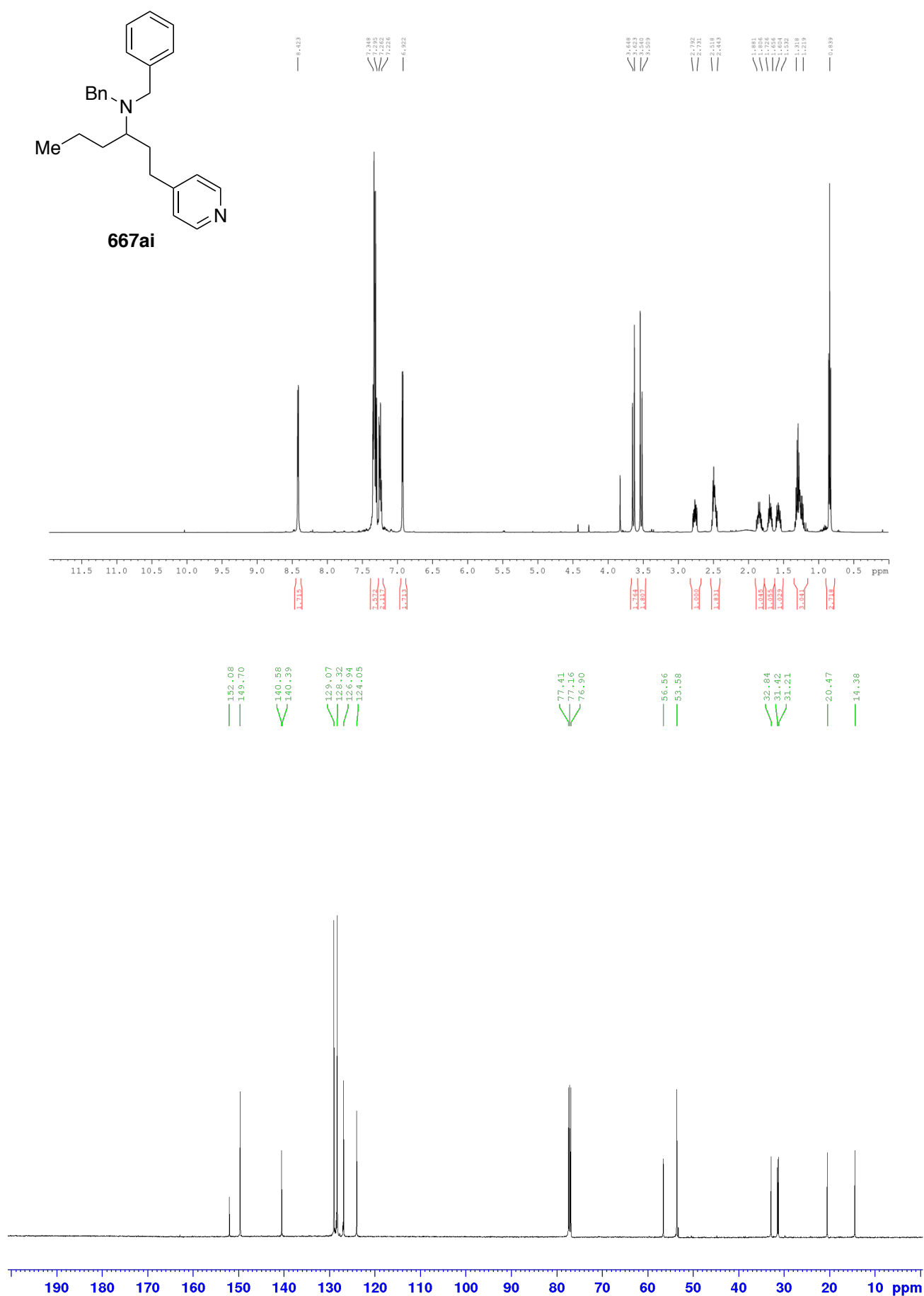


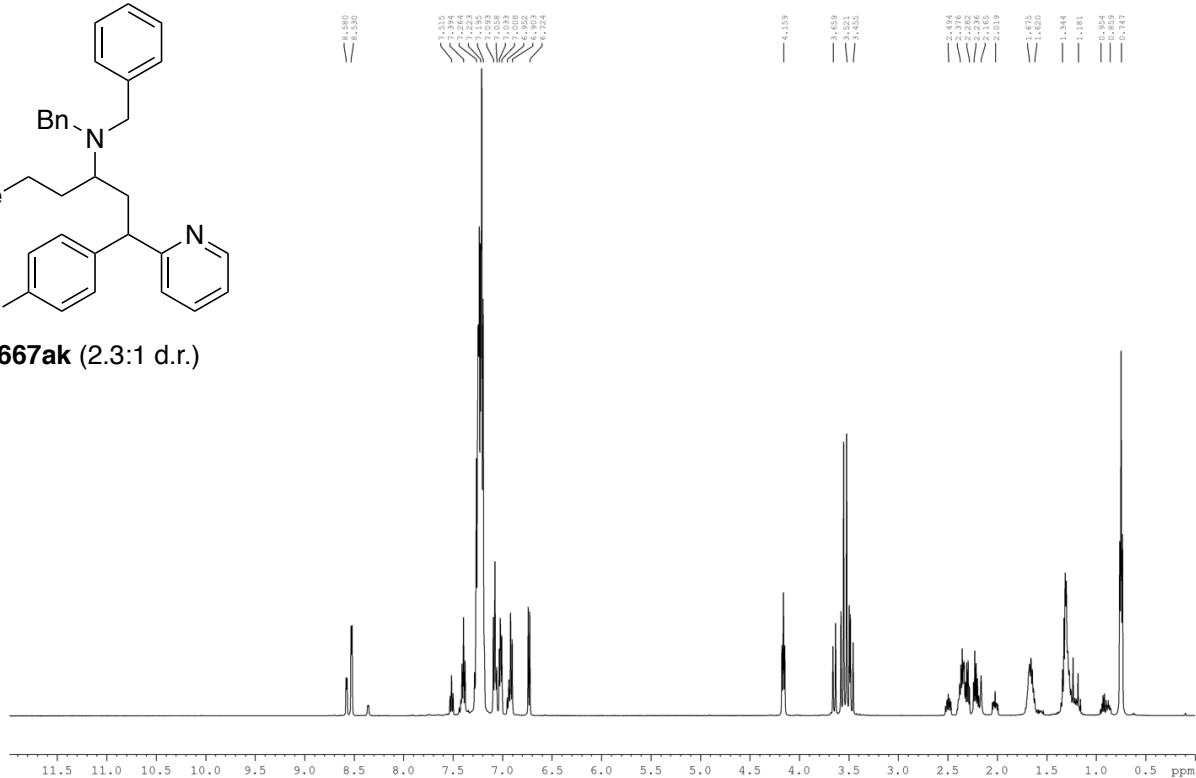
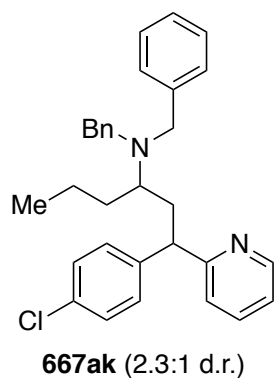


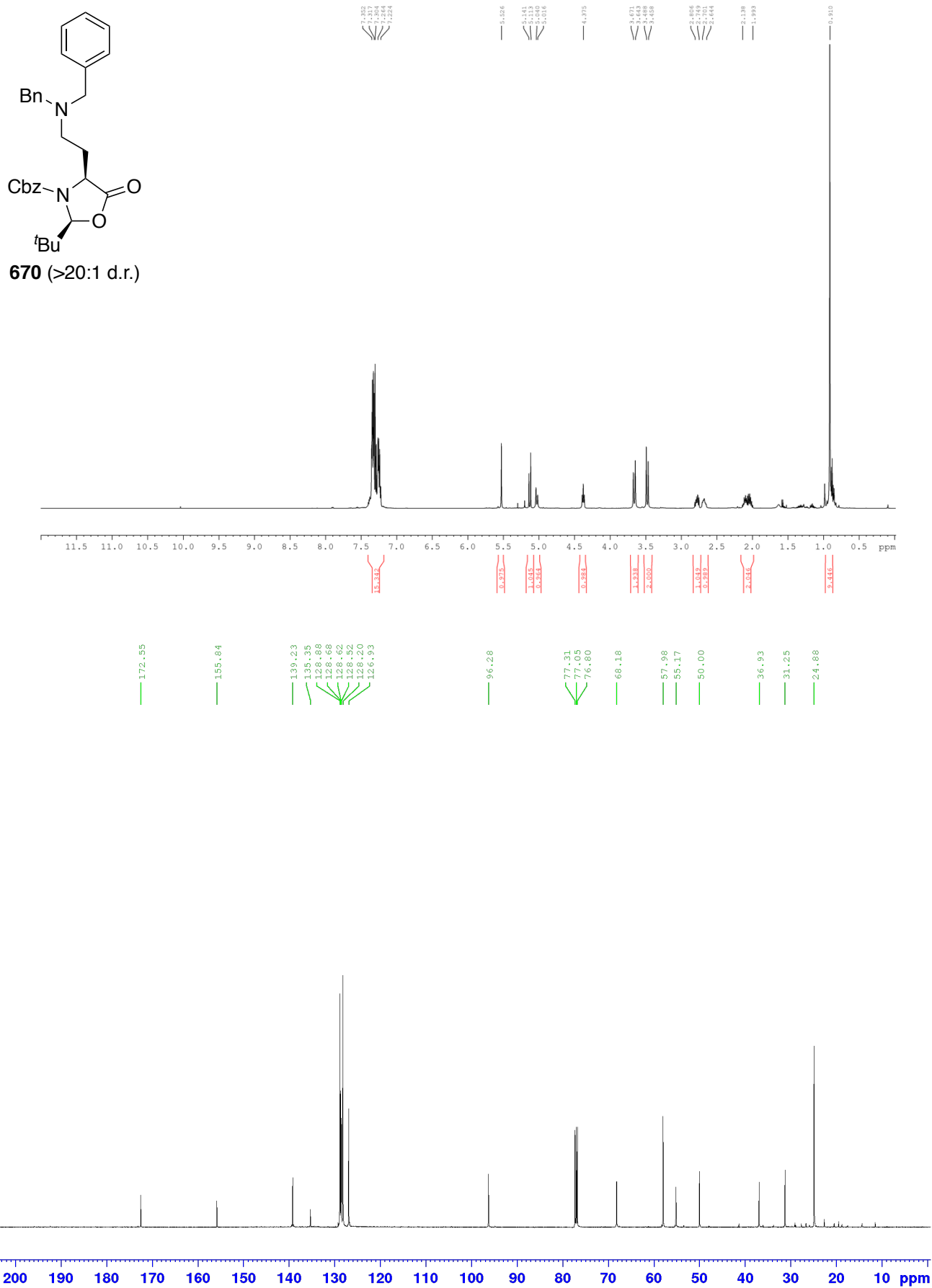


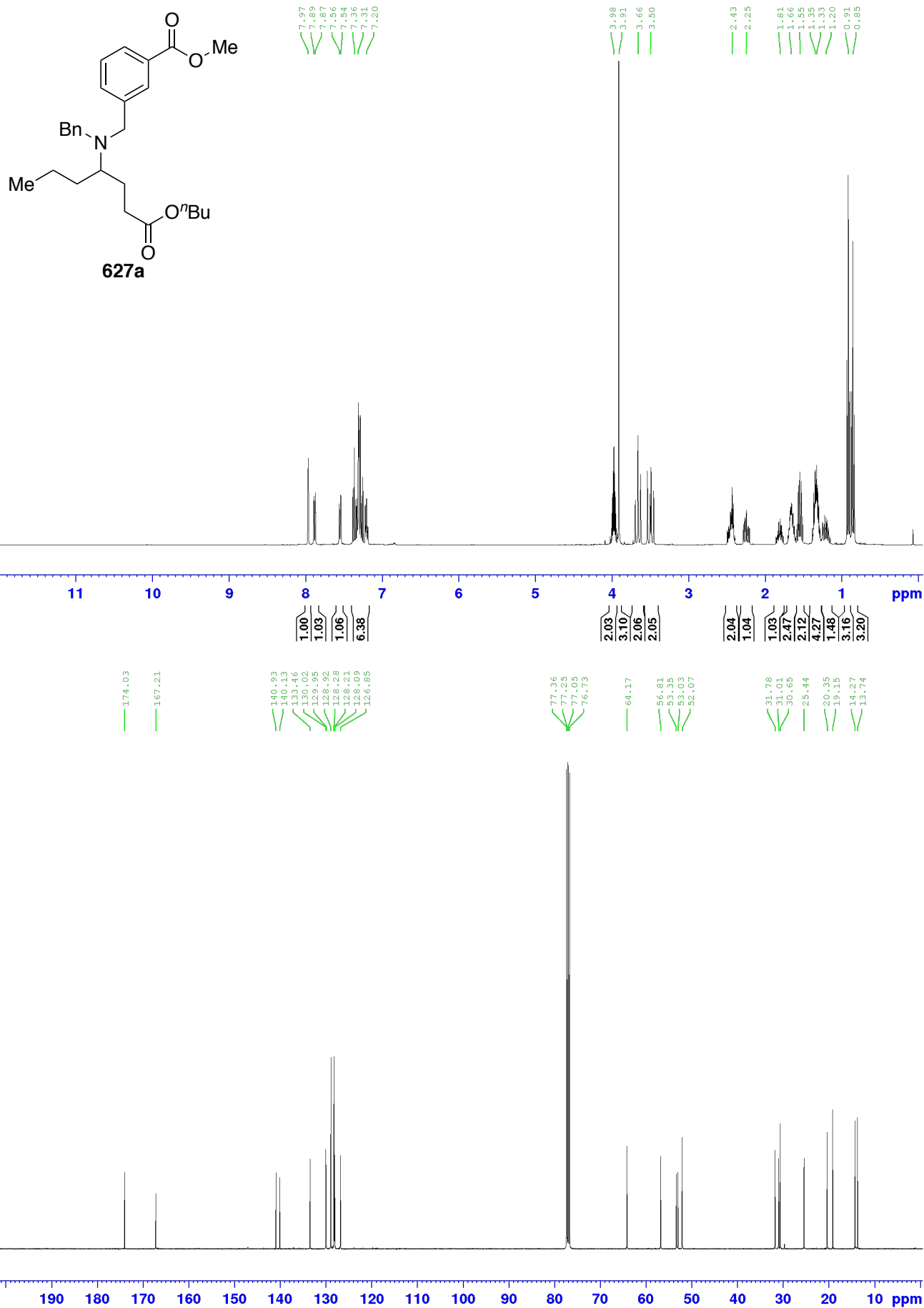


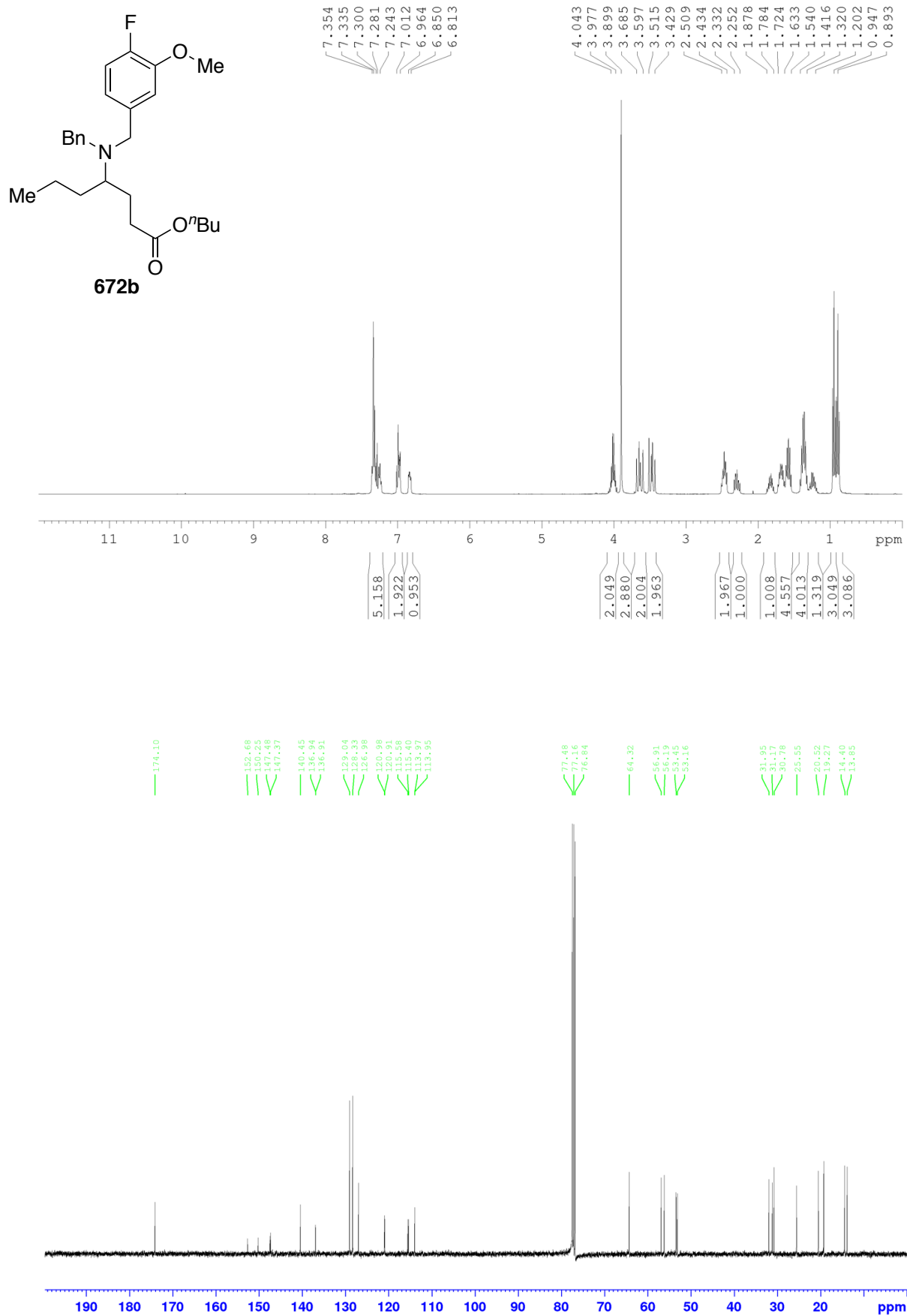




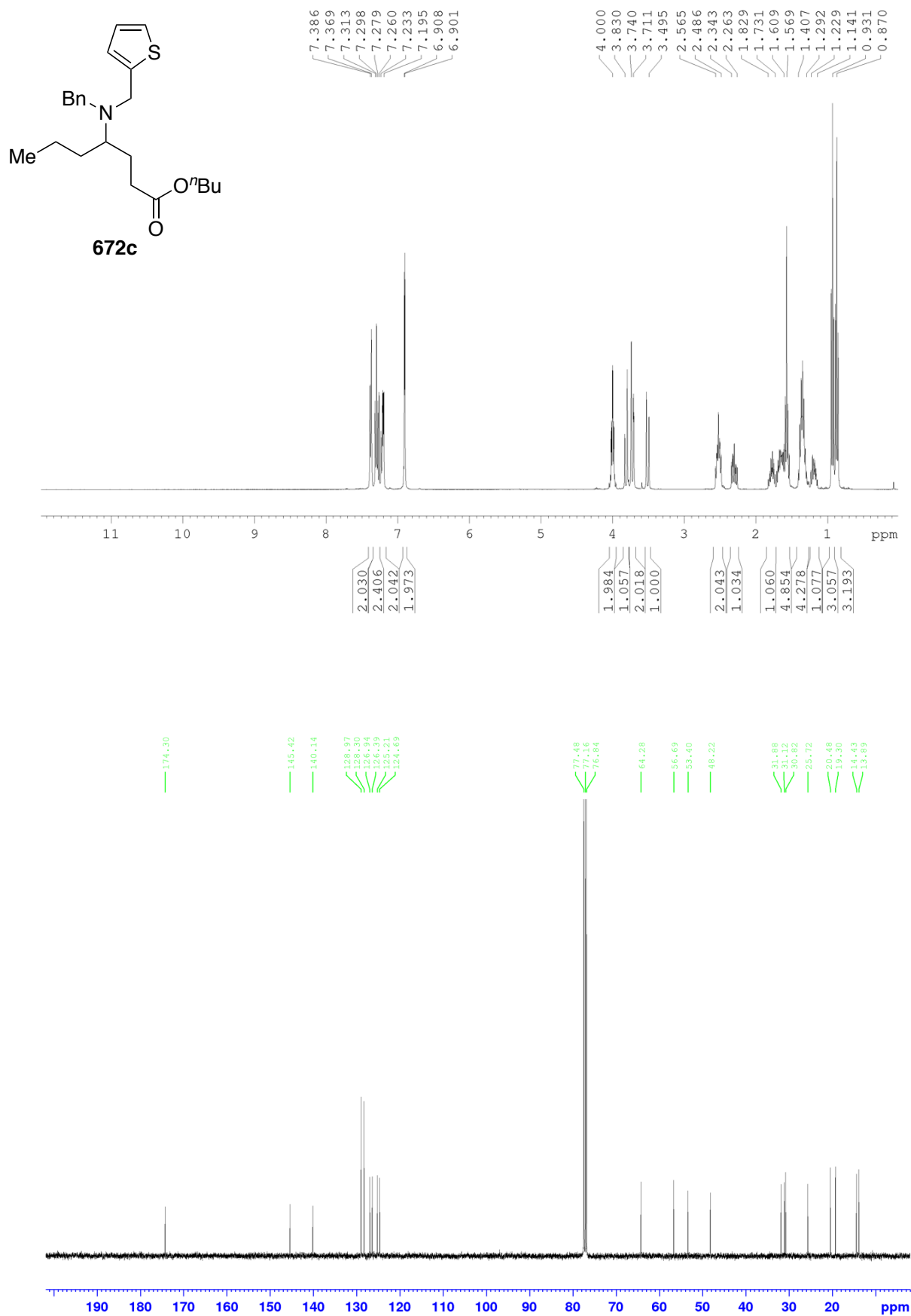


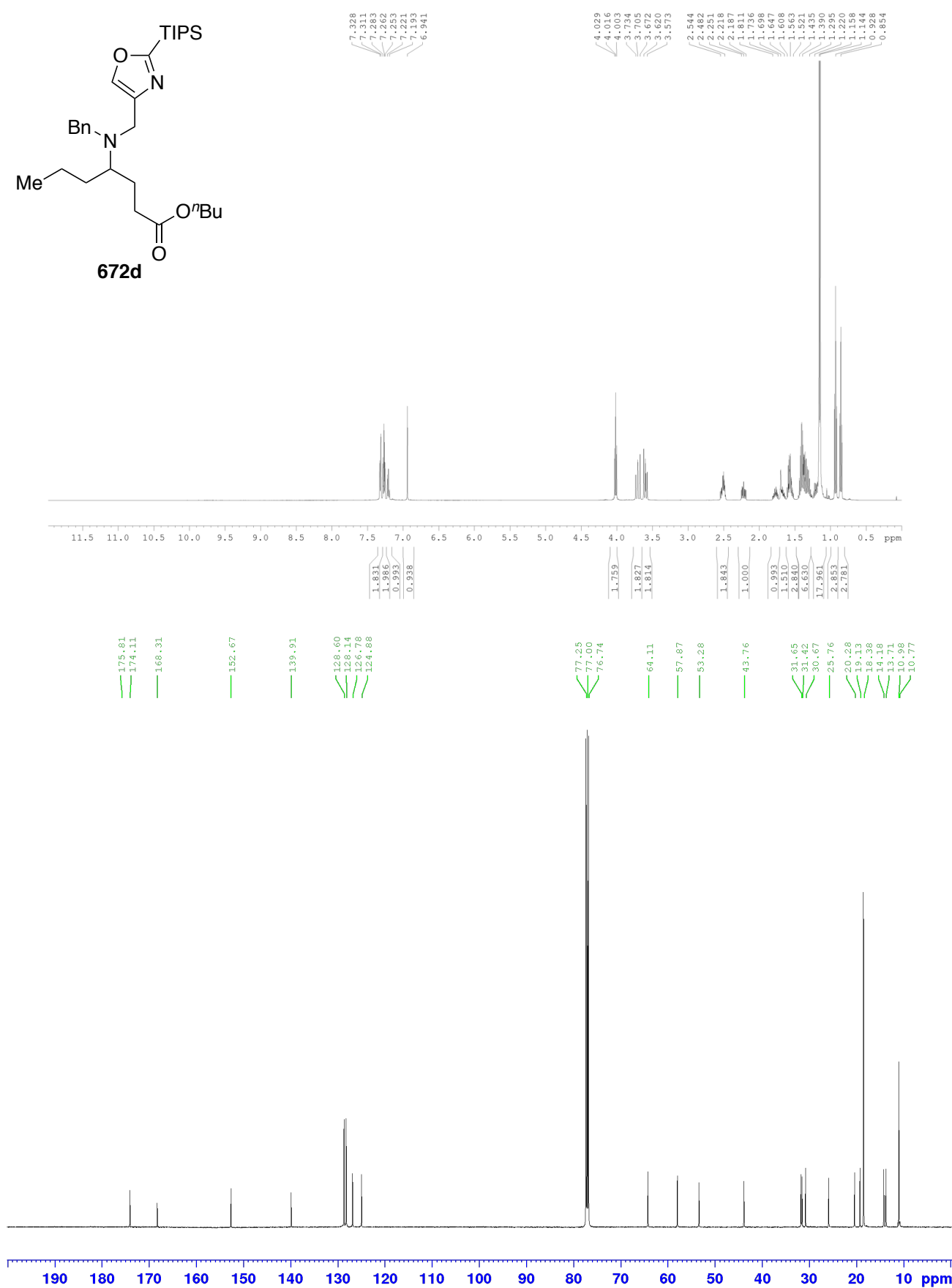


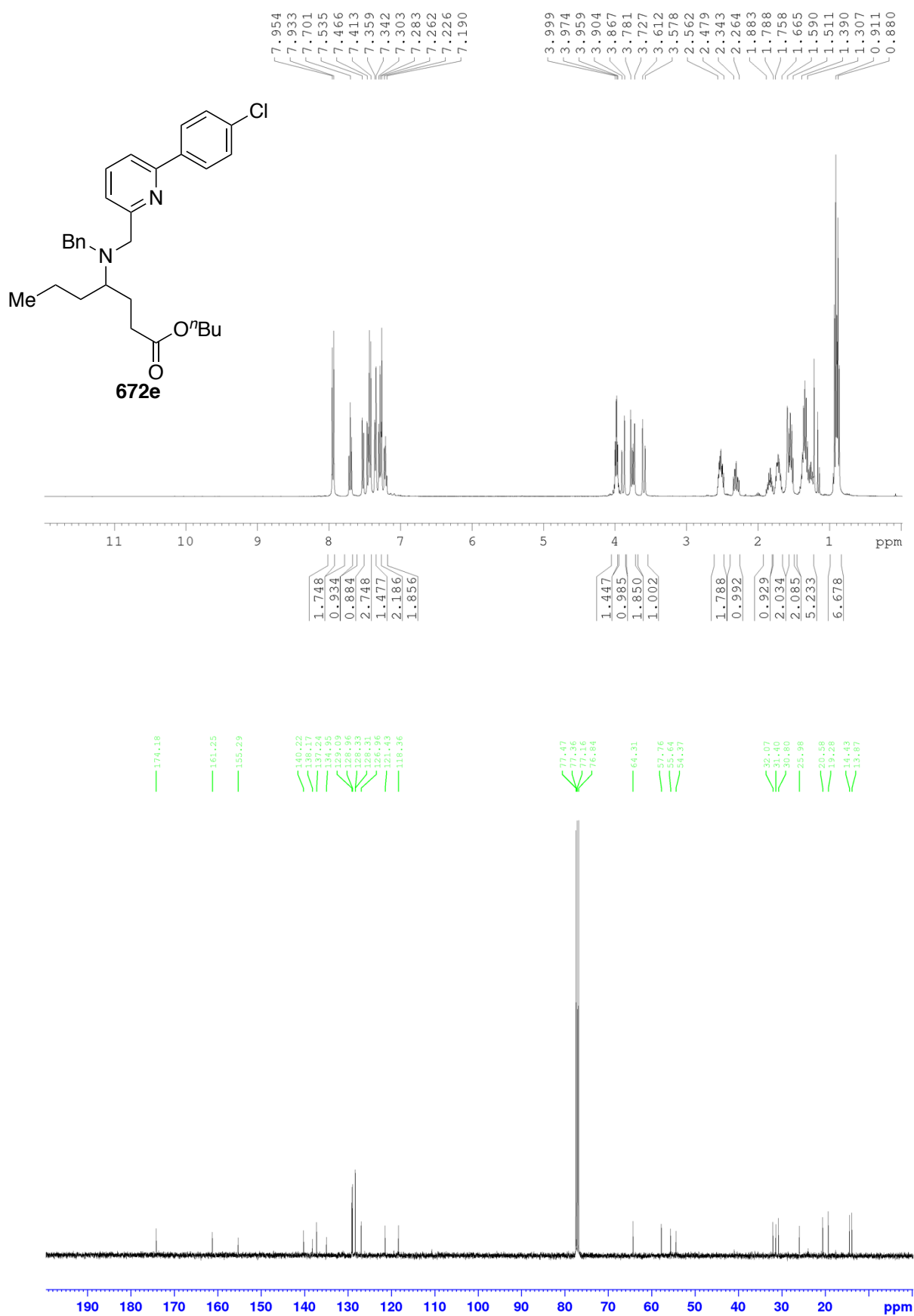


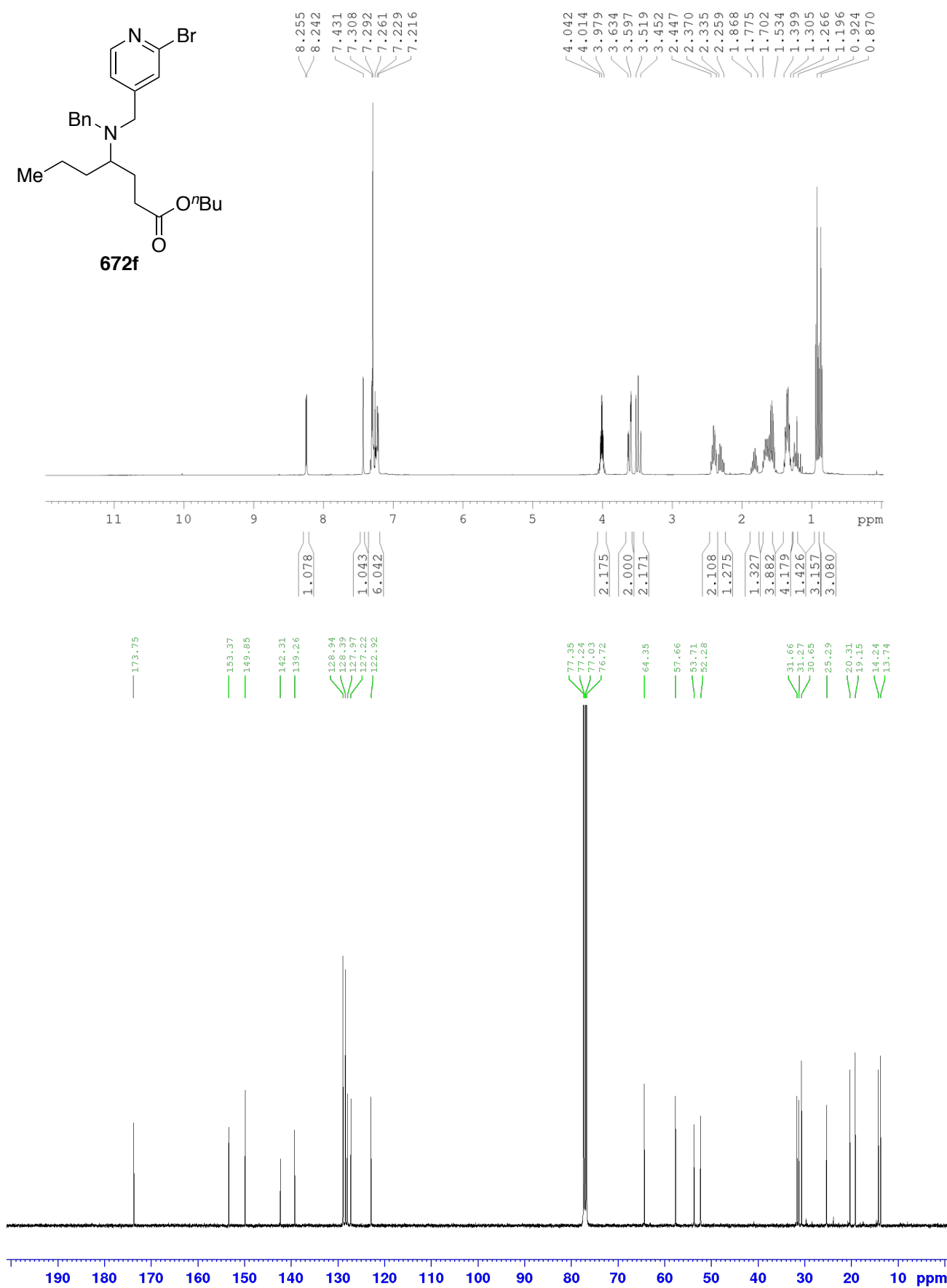


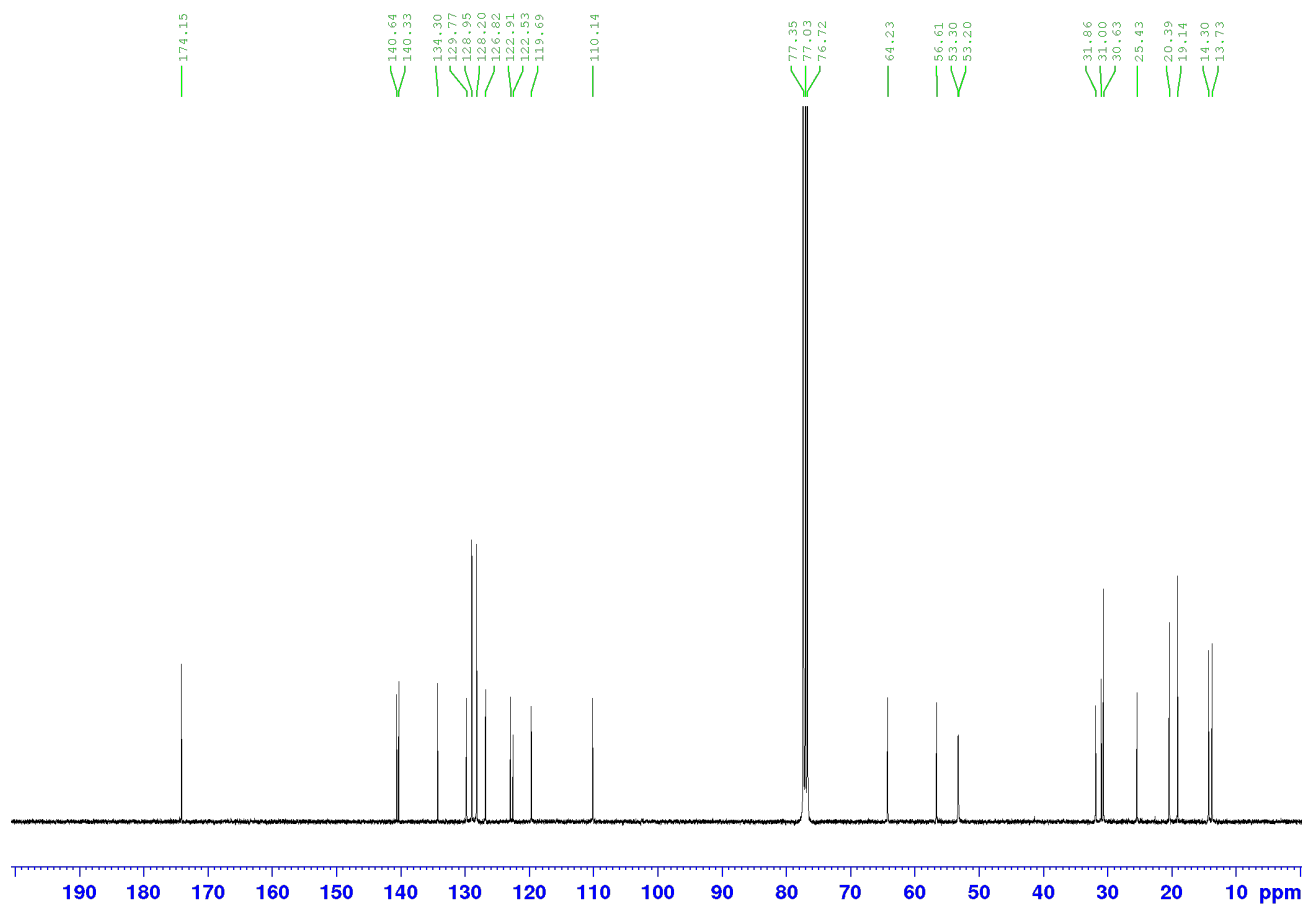
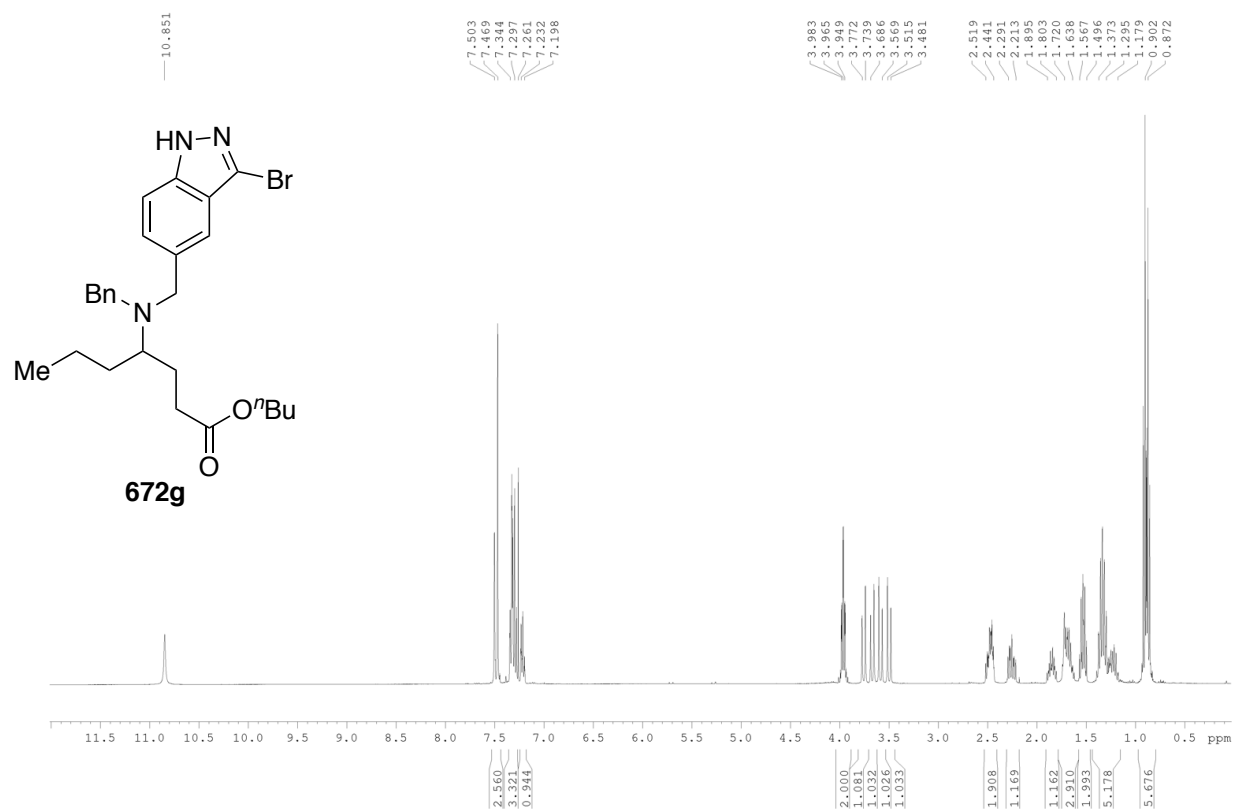


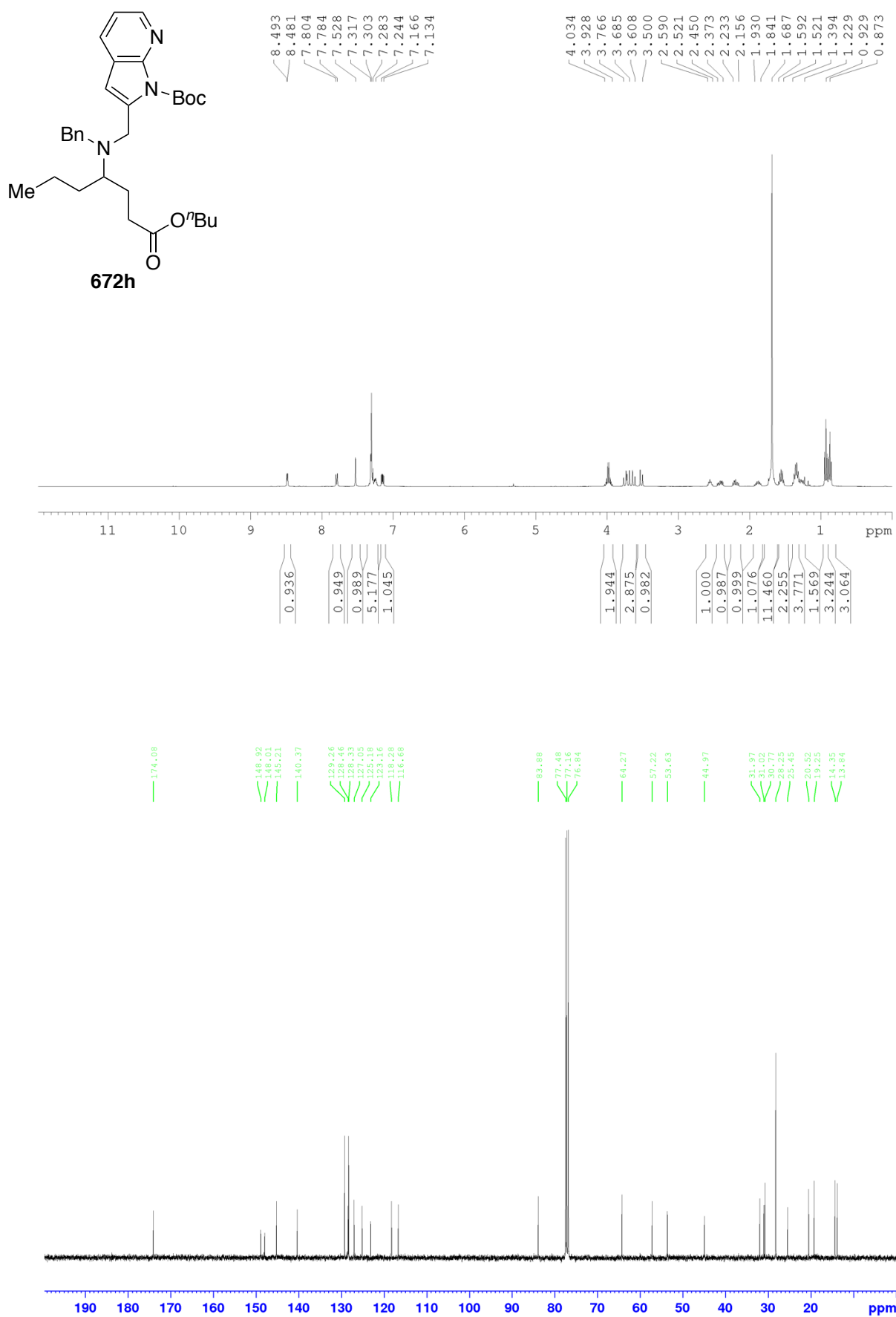


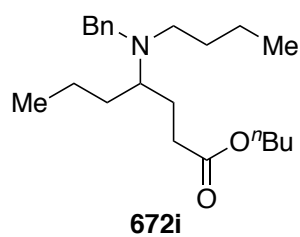












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7.279  
7.261  
7.217  
7.200  
7.184

4.030

3.670

3.455

2.503

2.396

2.262

1.707

1.607

1.584

1.533

1.418

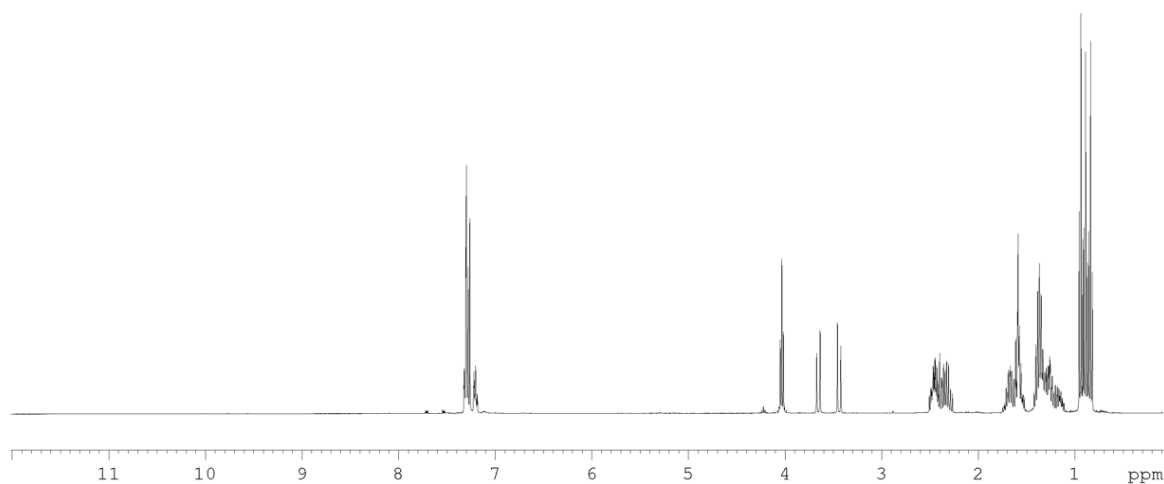
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1.258

1.123

0.933

0.884



174.40

141.25

128.69

128.01

126.46

77.34

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48.87

31.89

31.14

31.11

30.71

25.86

20.92

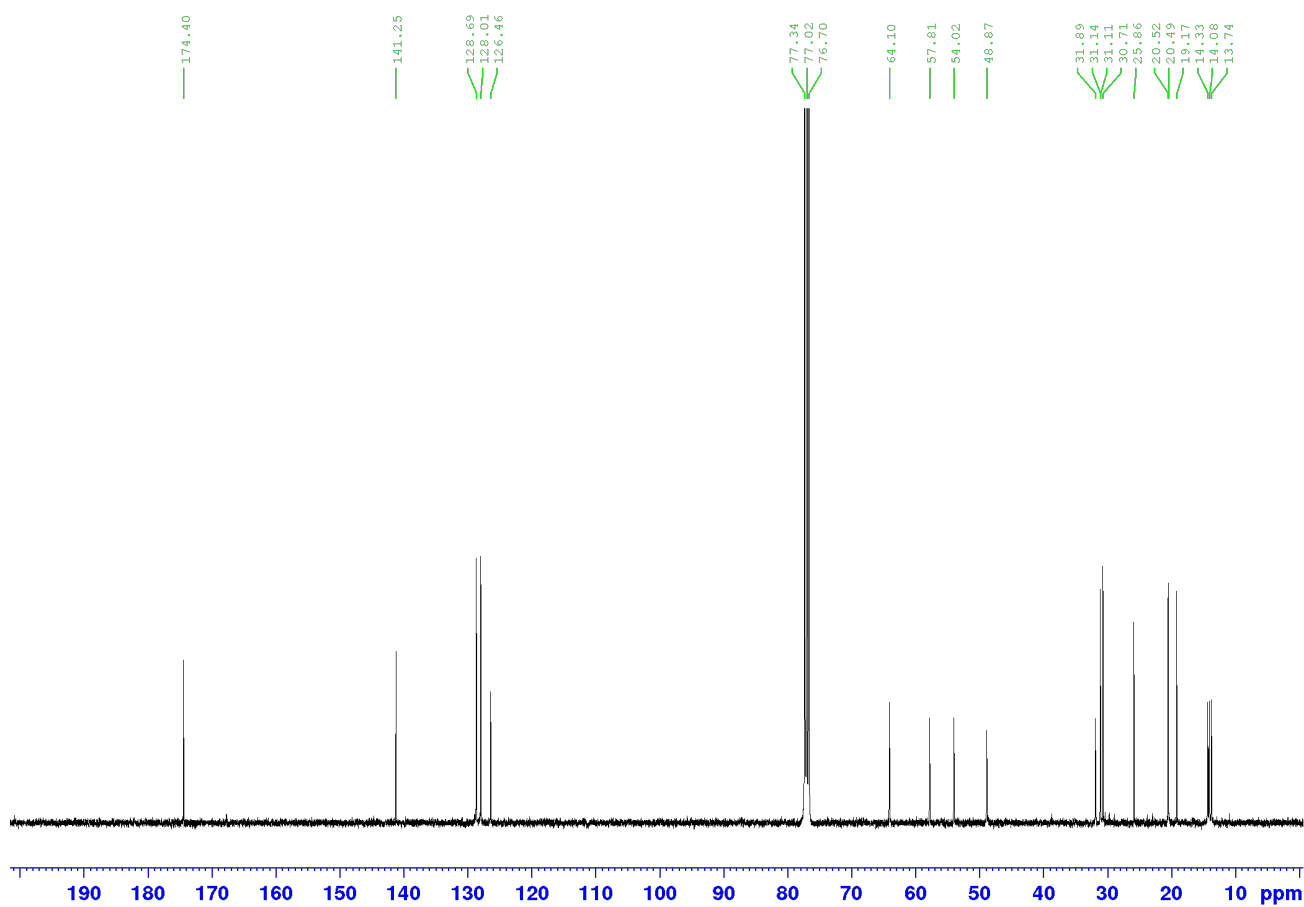
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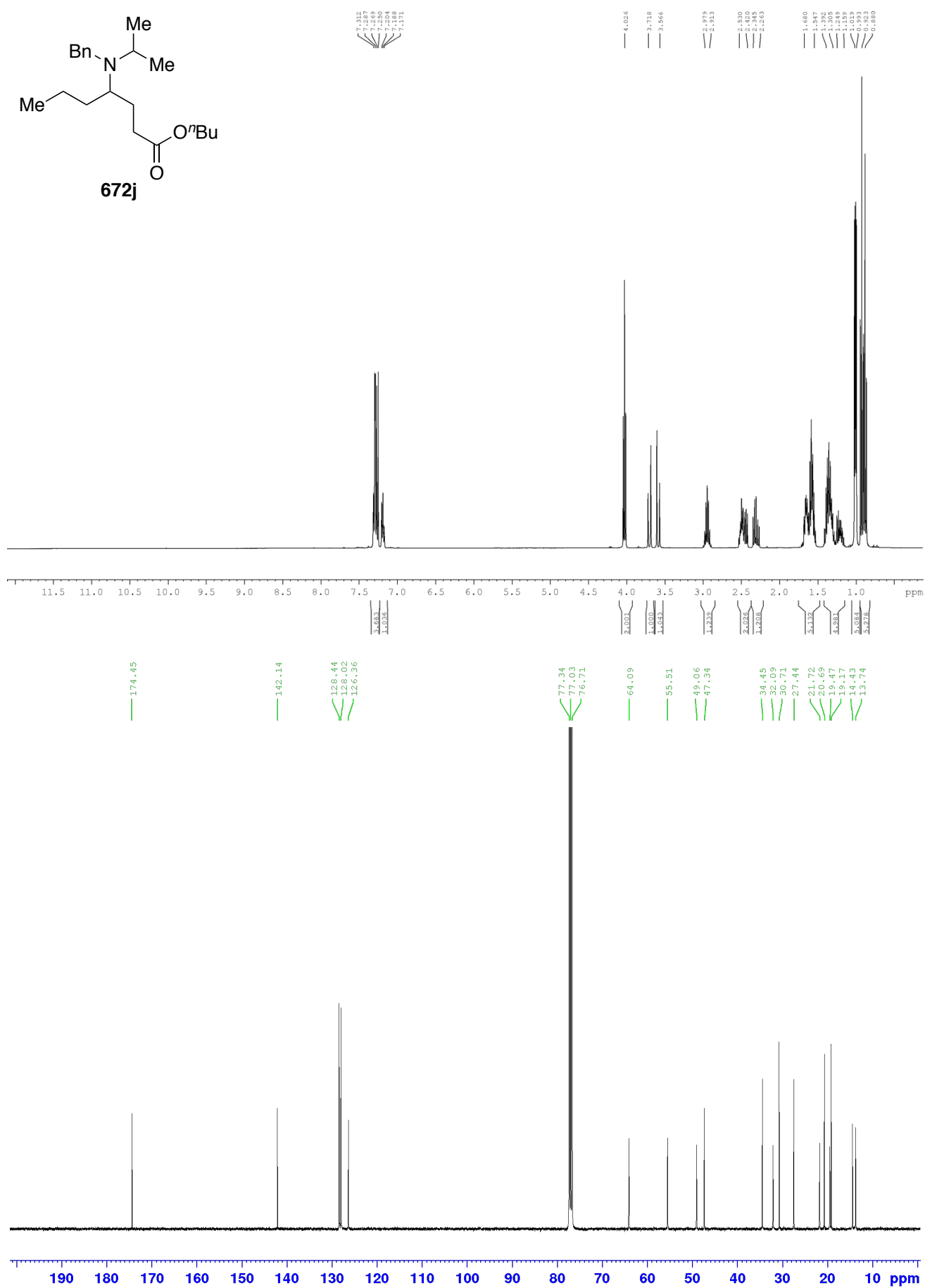
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14.33

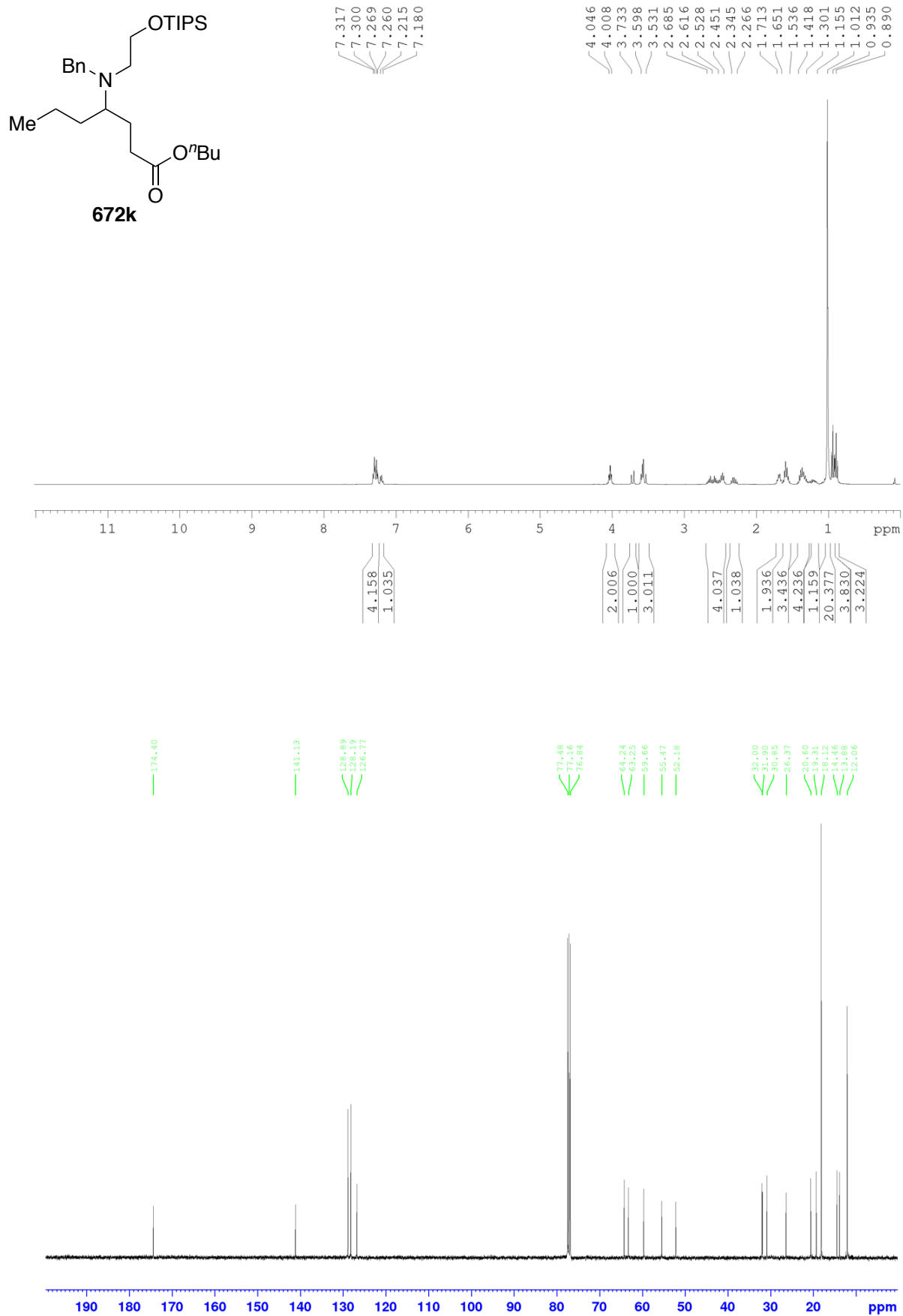
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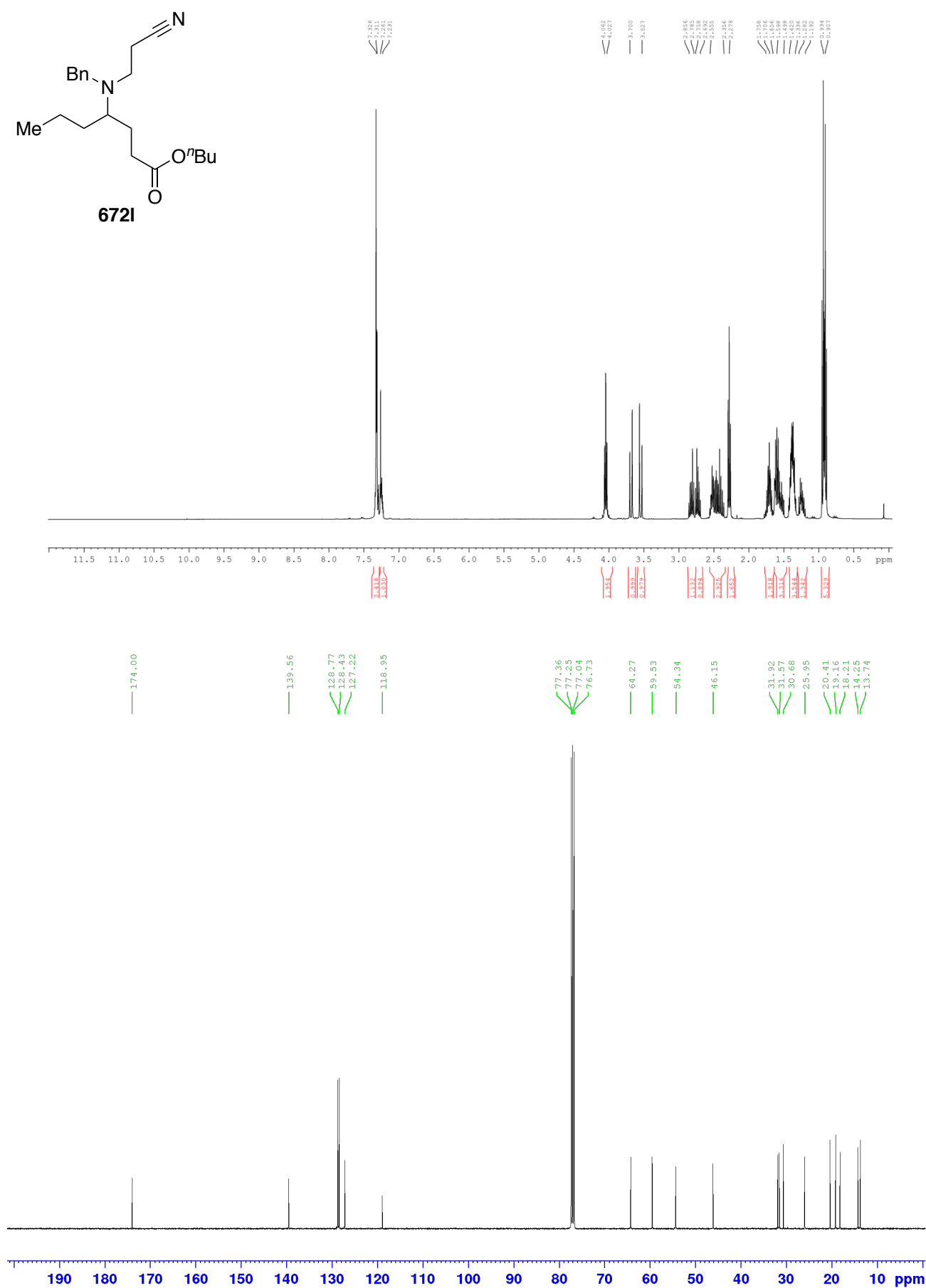
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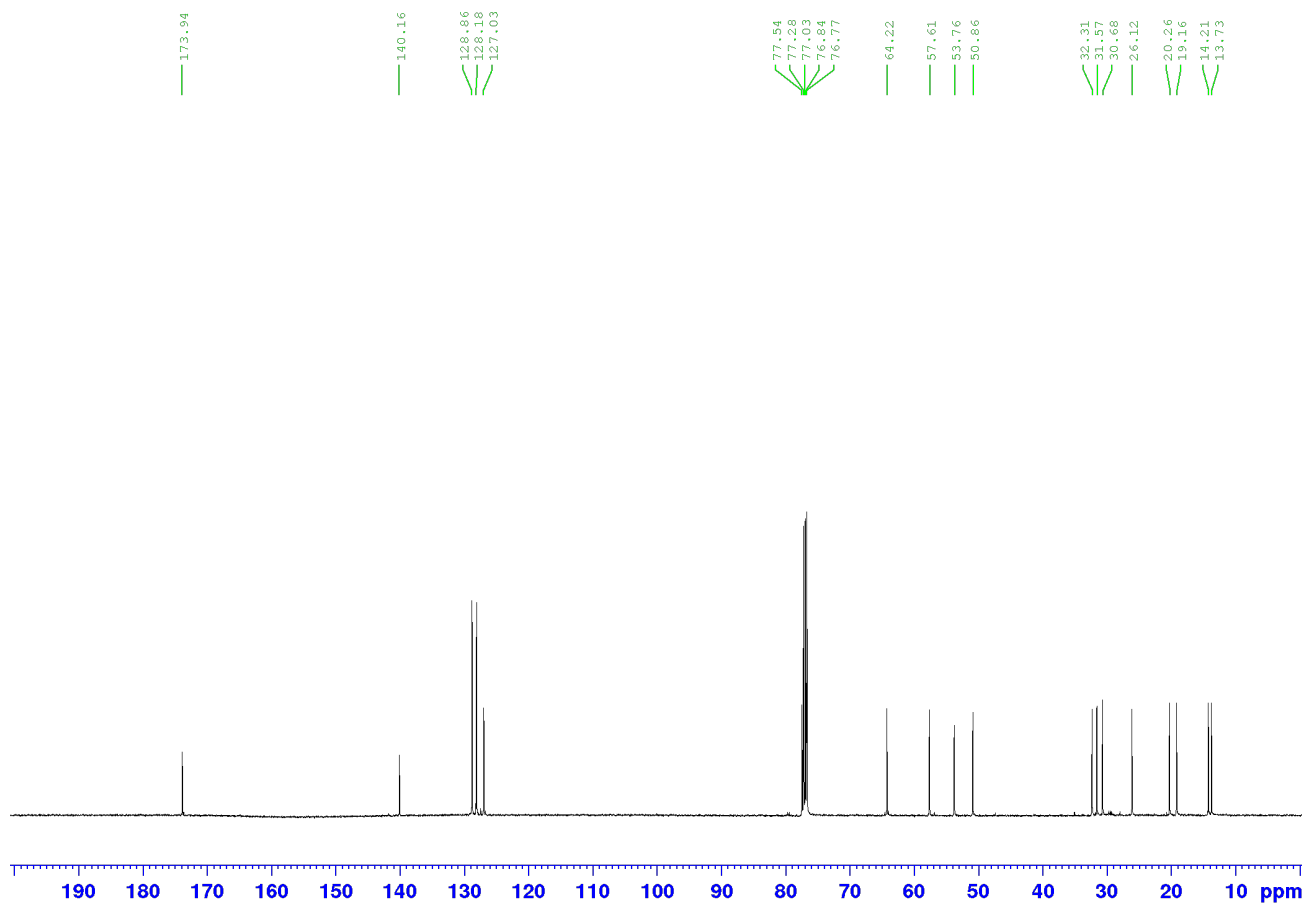
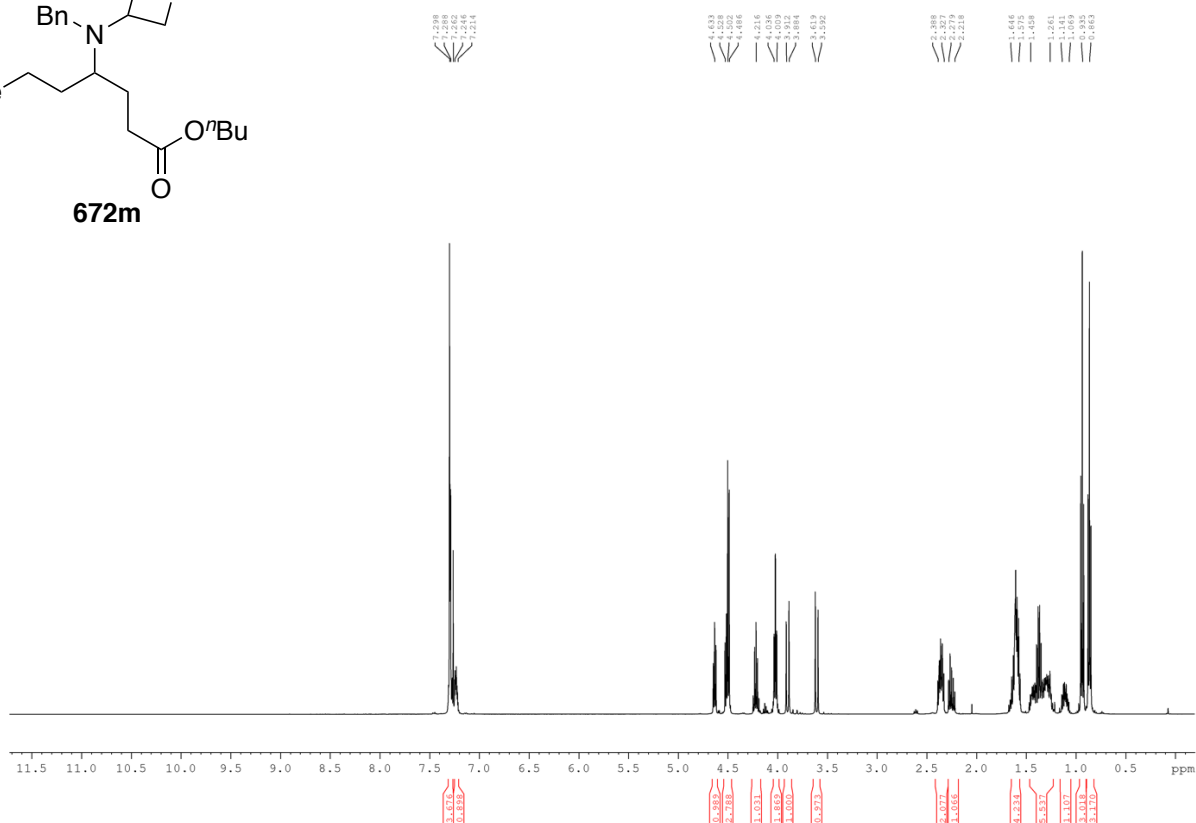
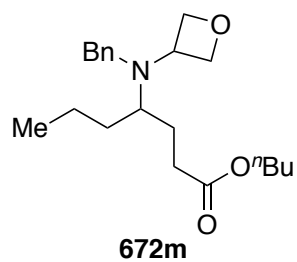


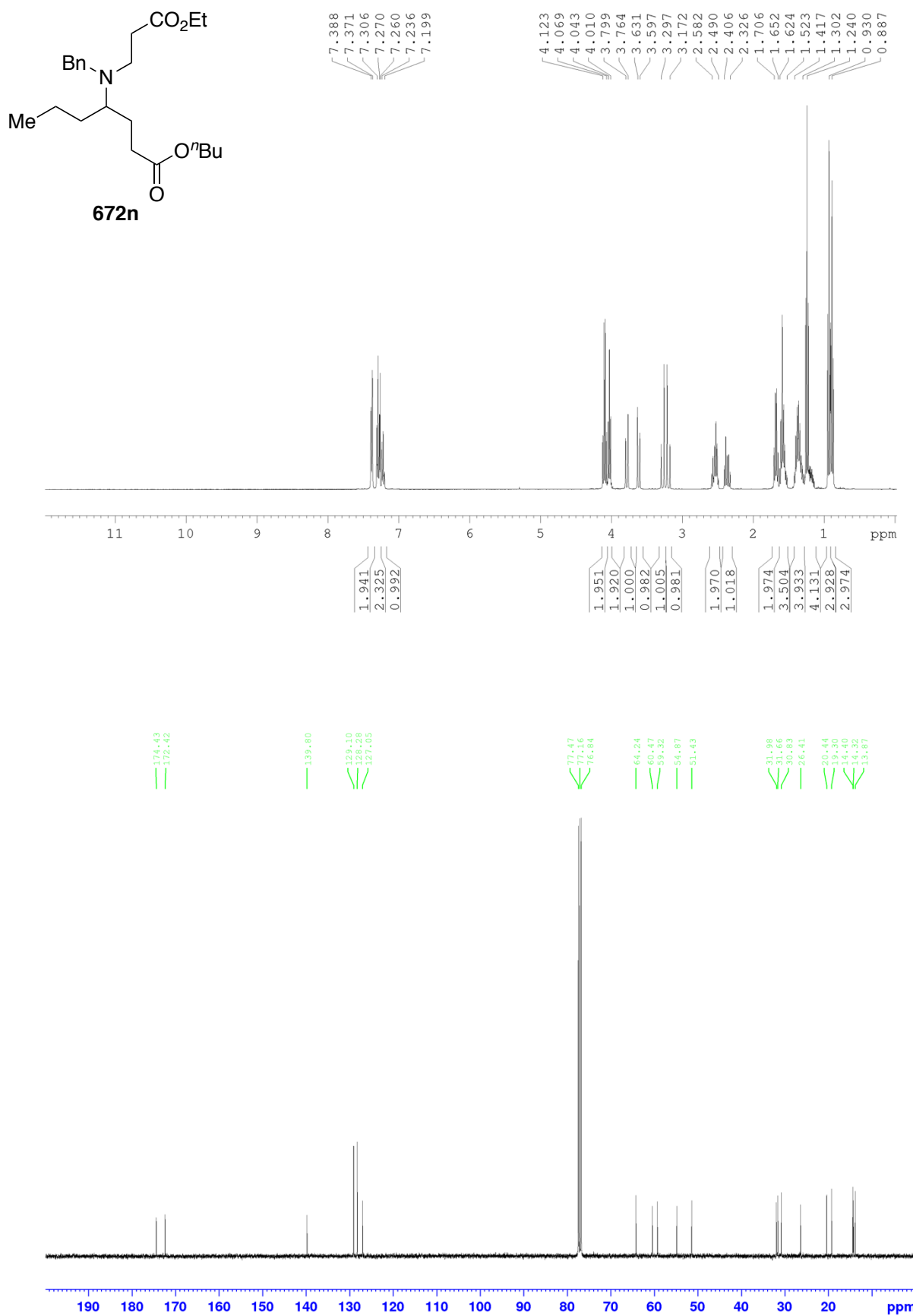


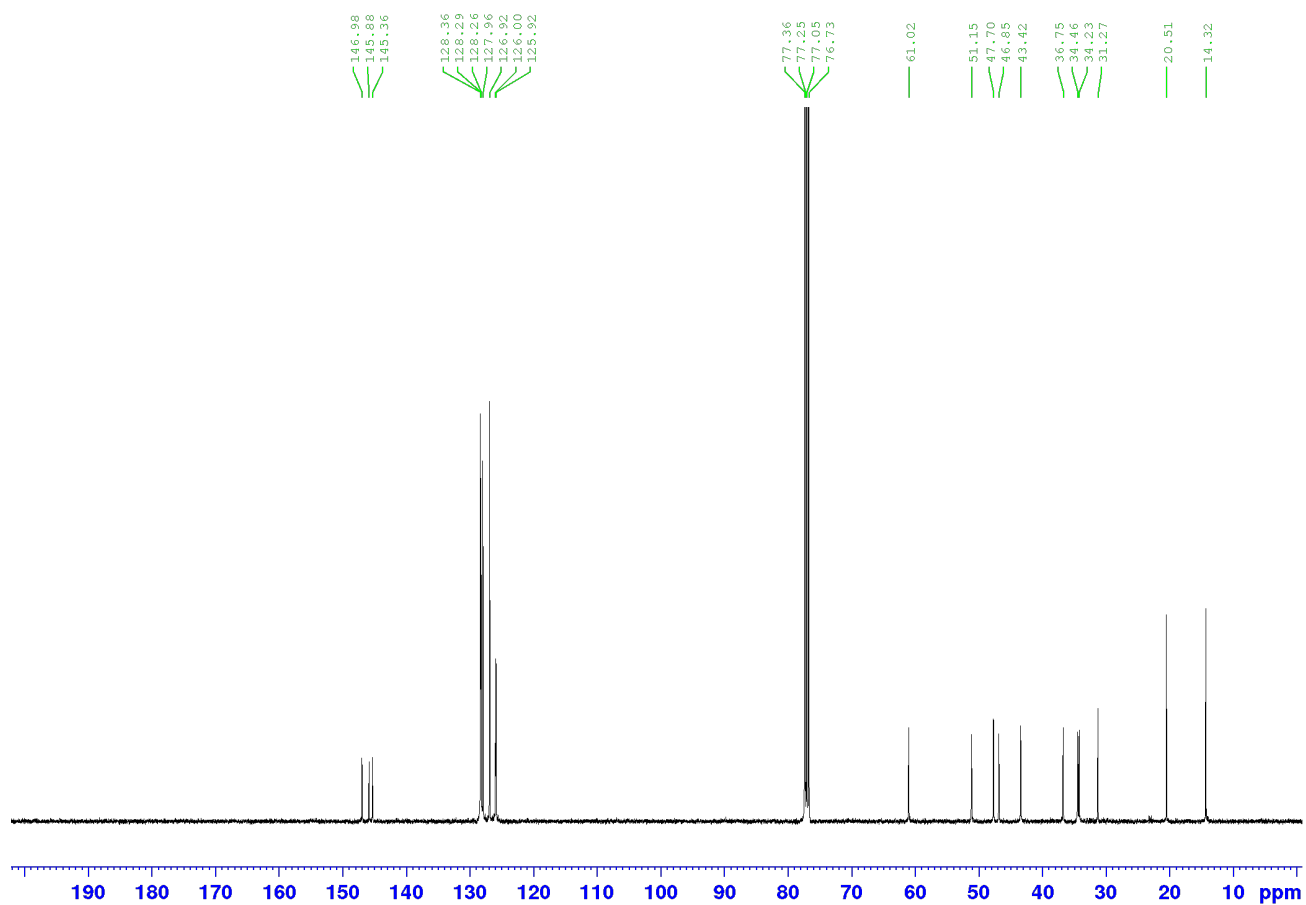
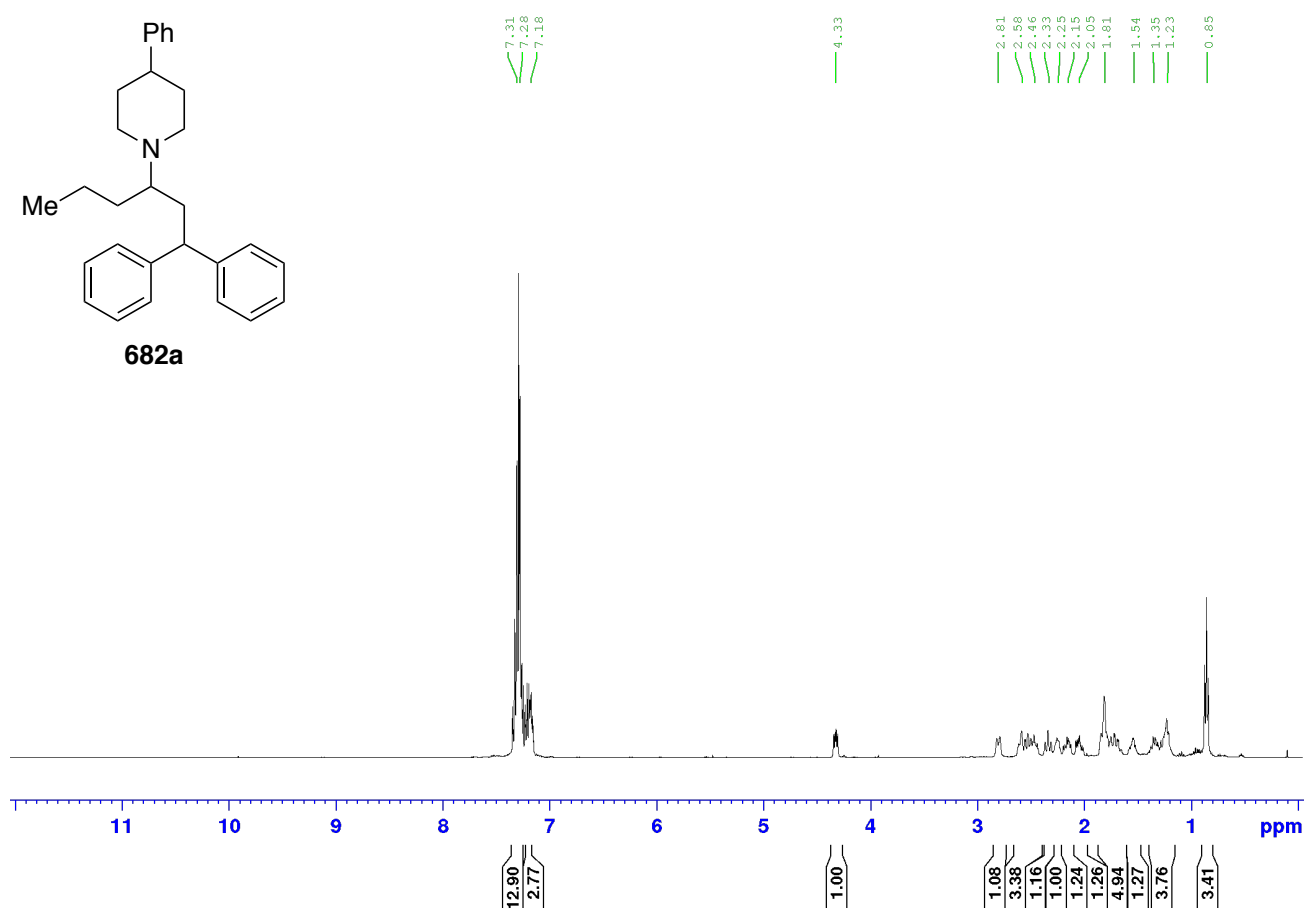
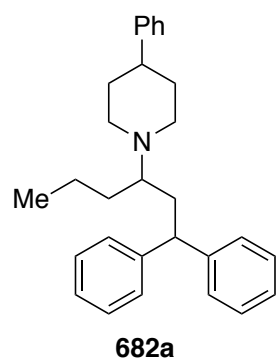


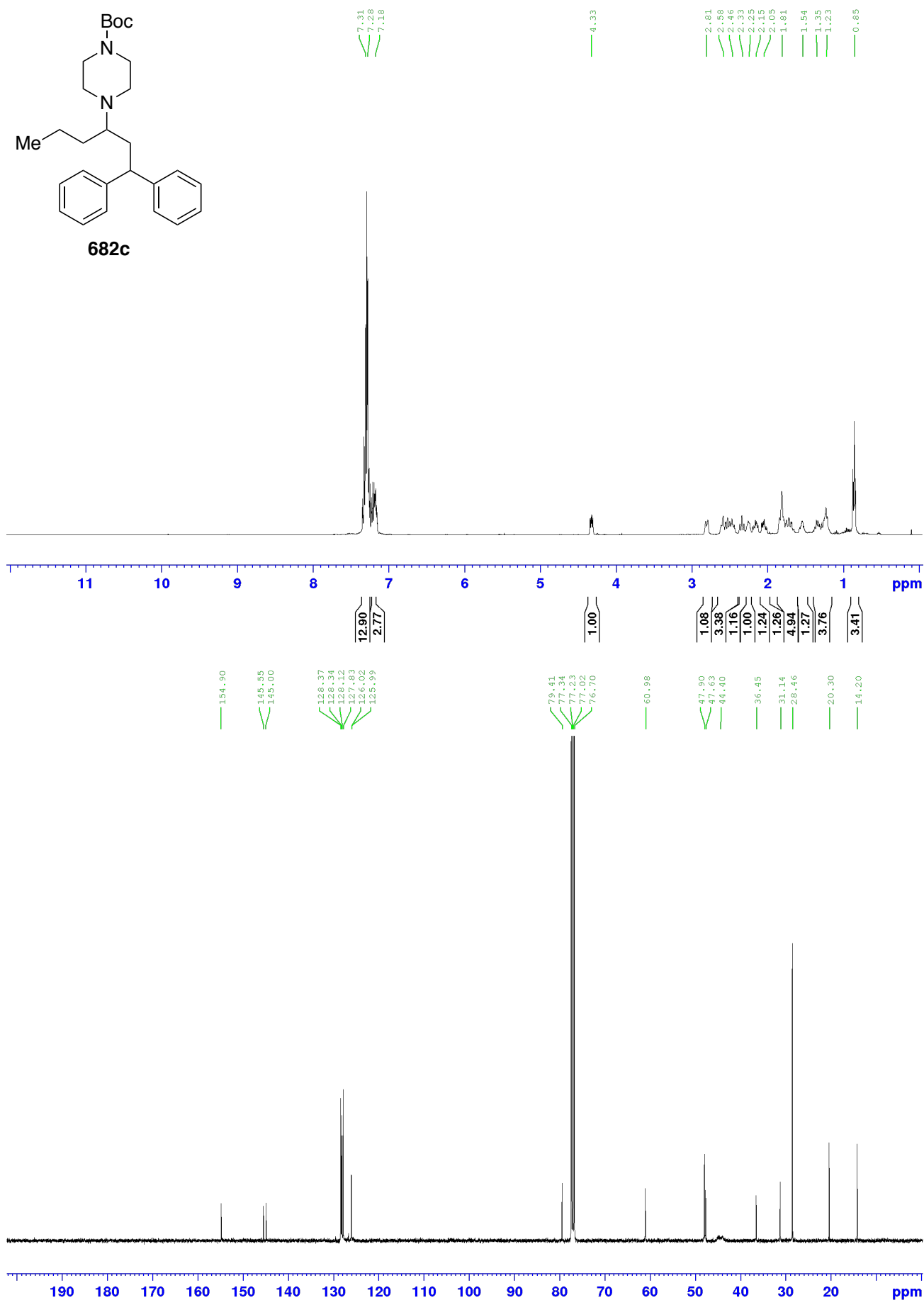


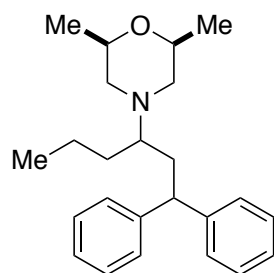




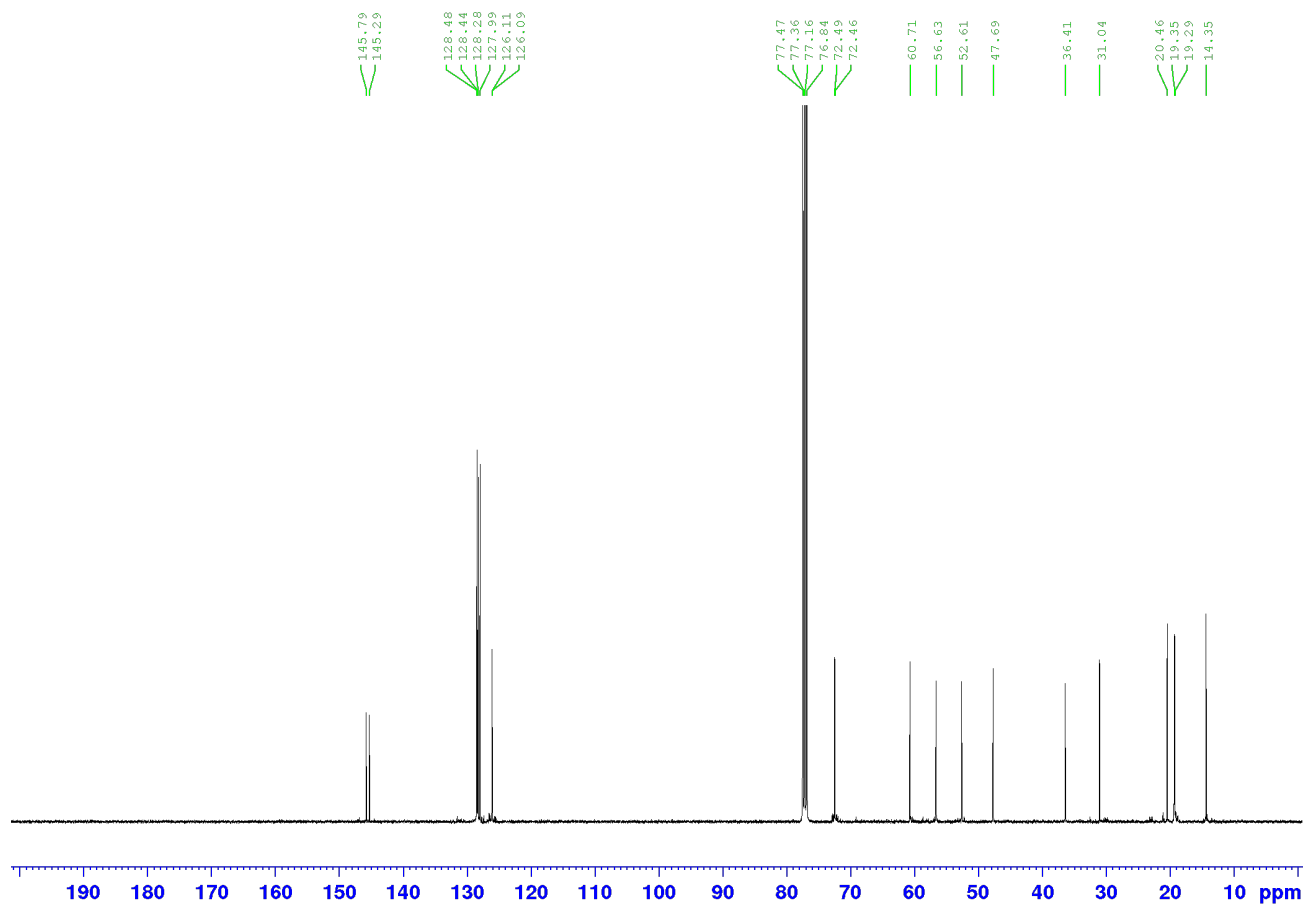
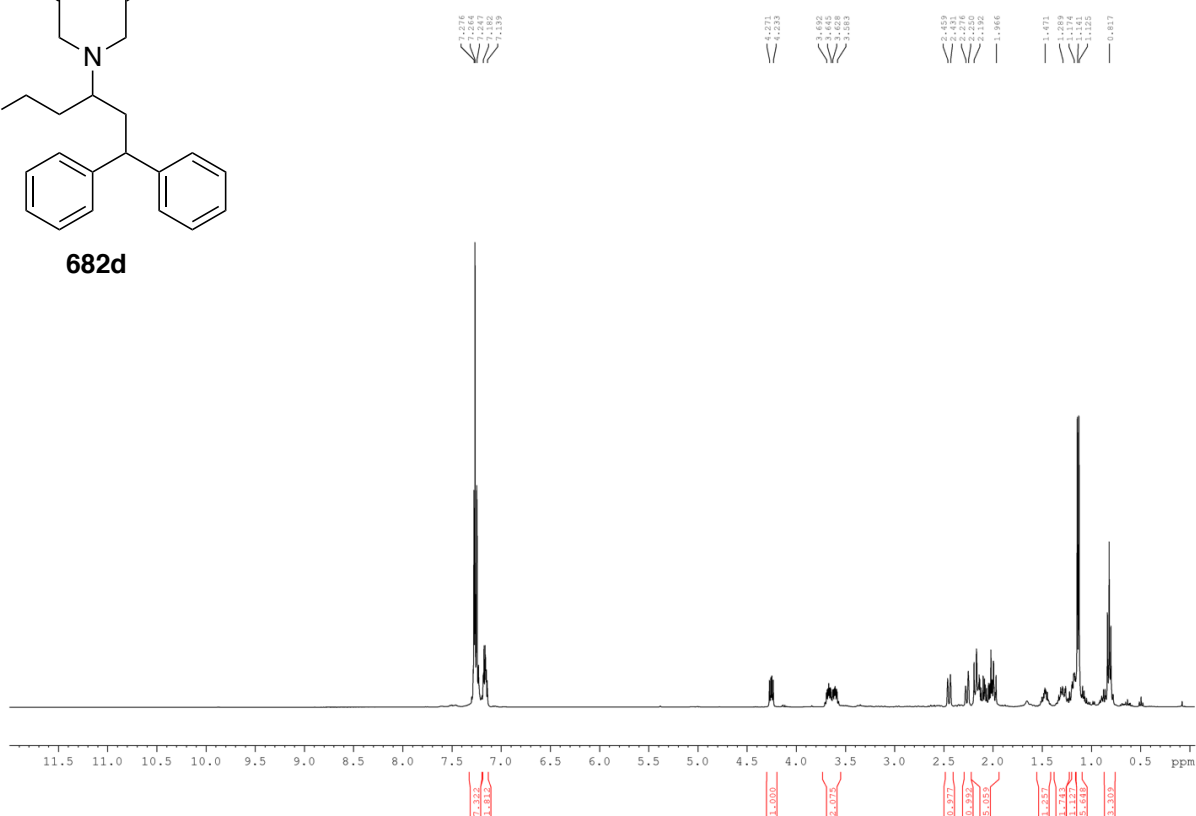


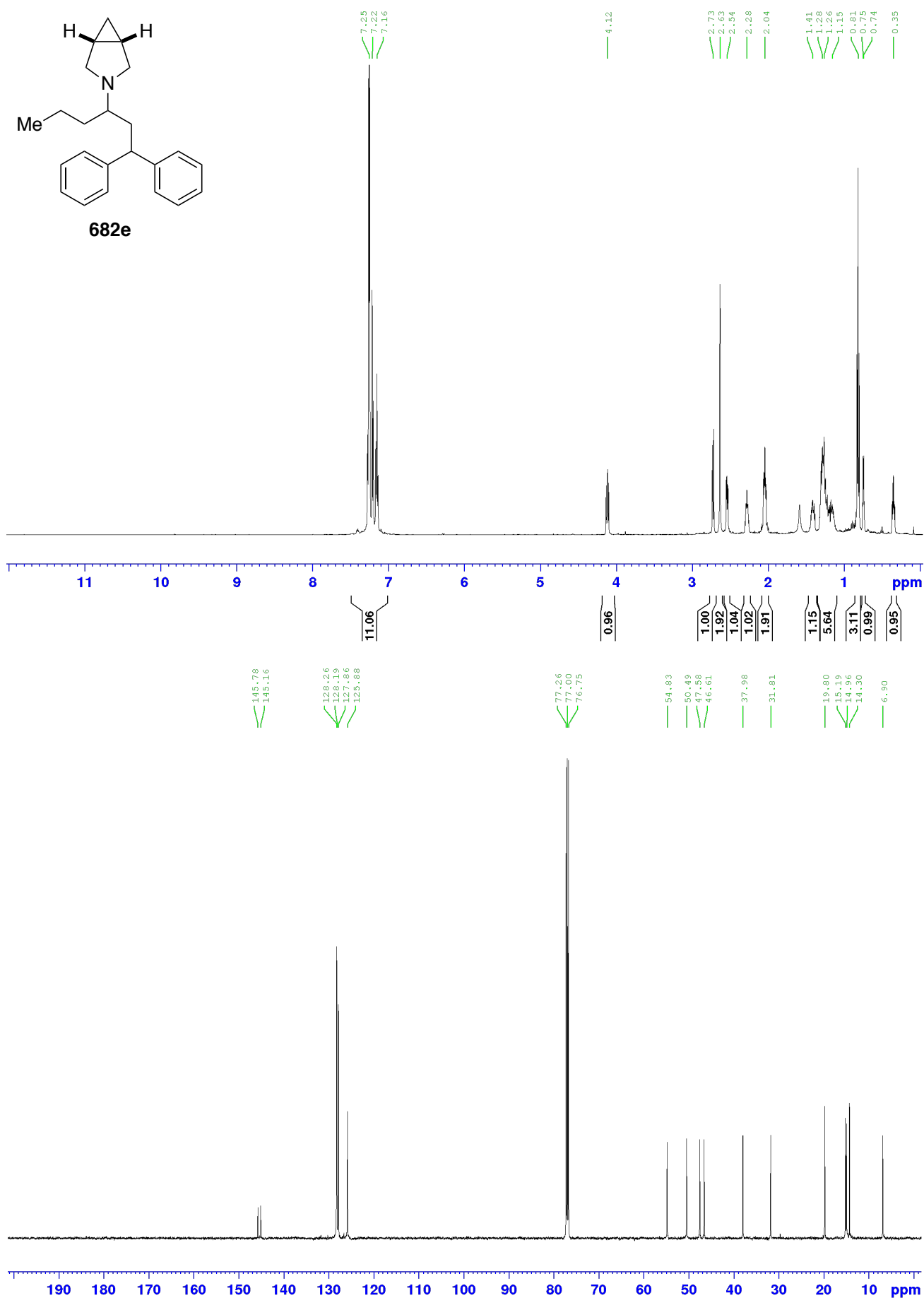




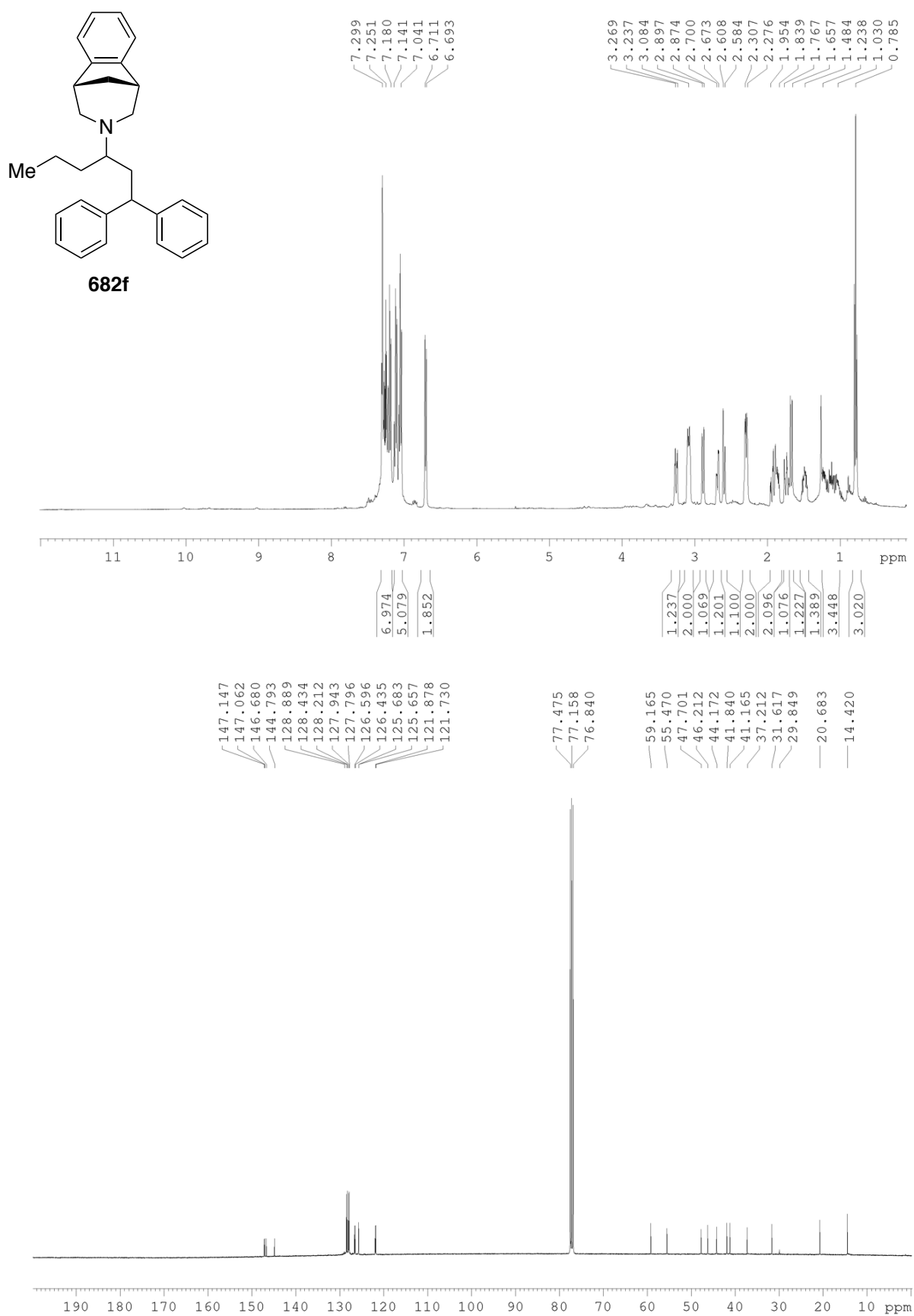


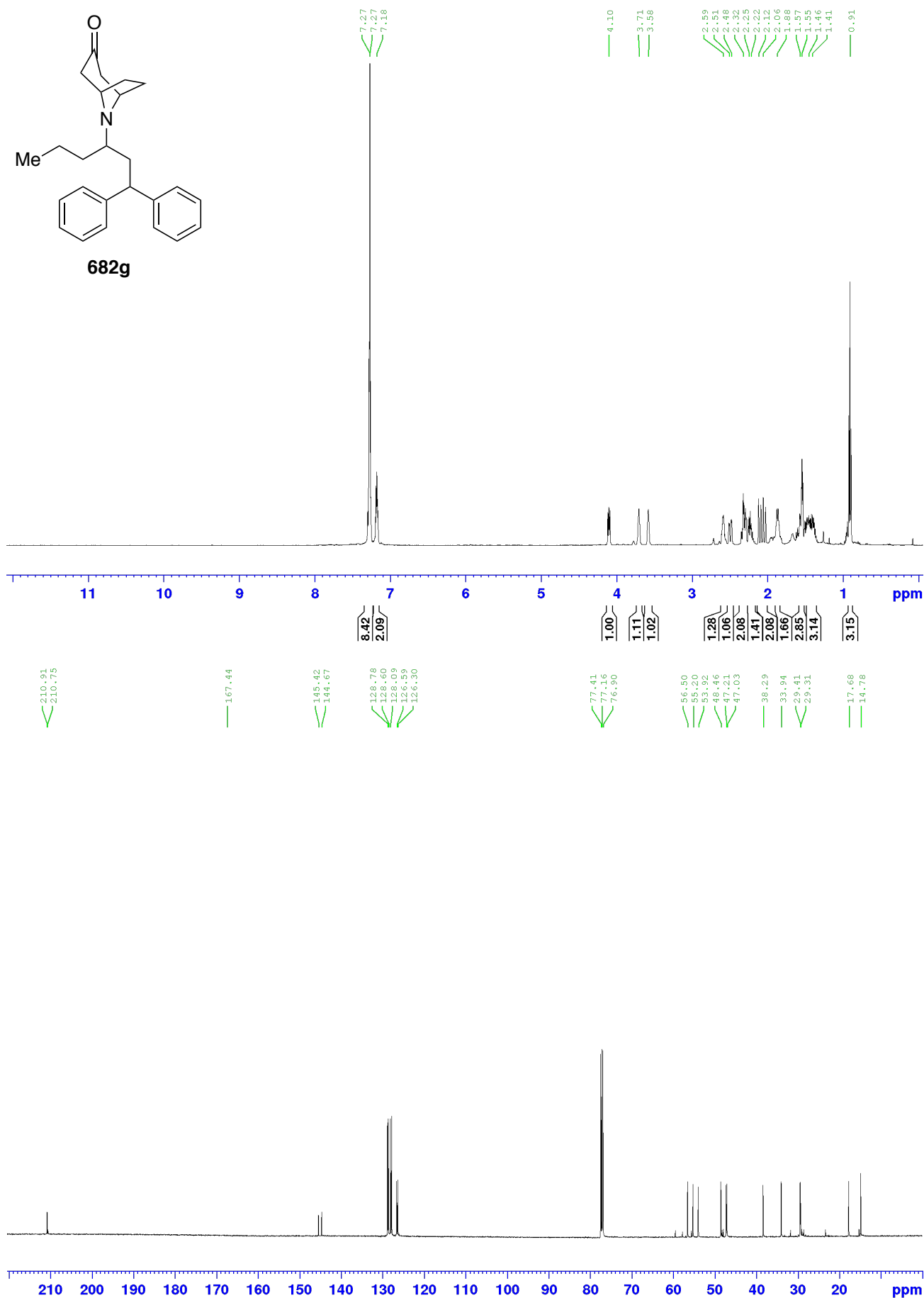
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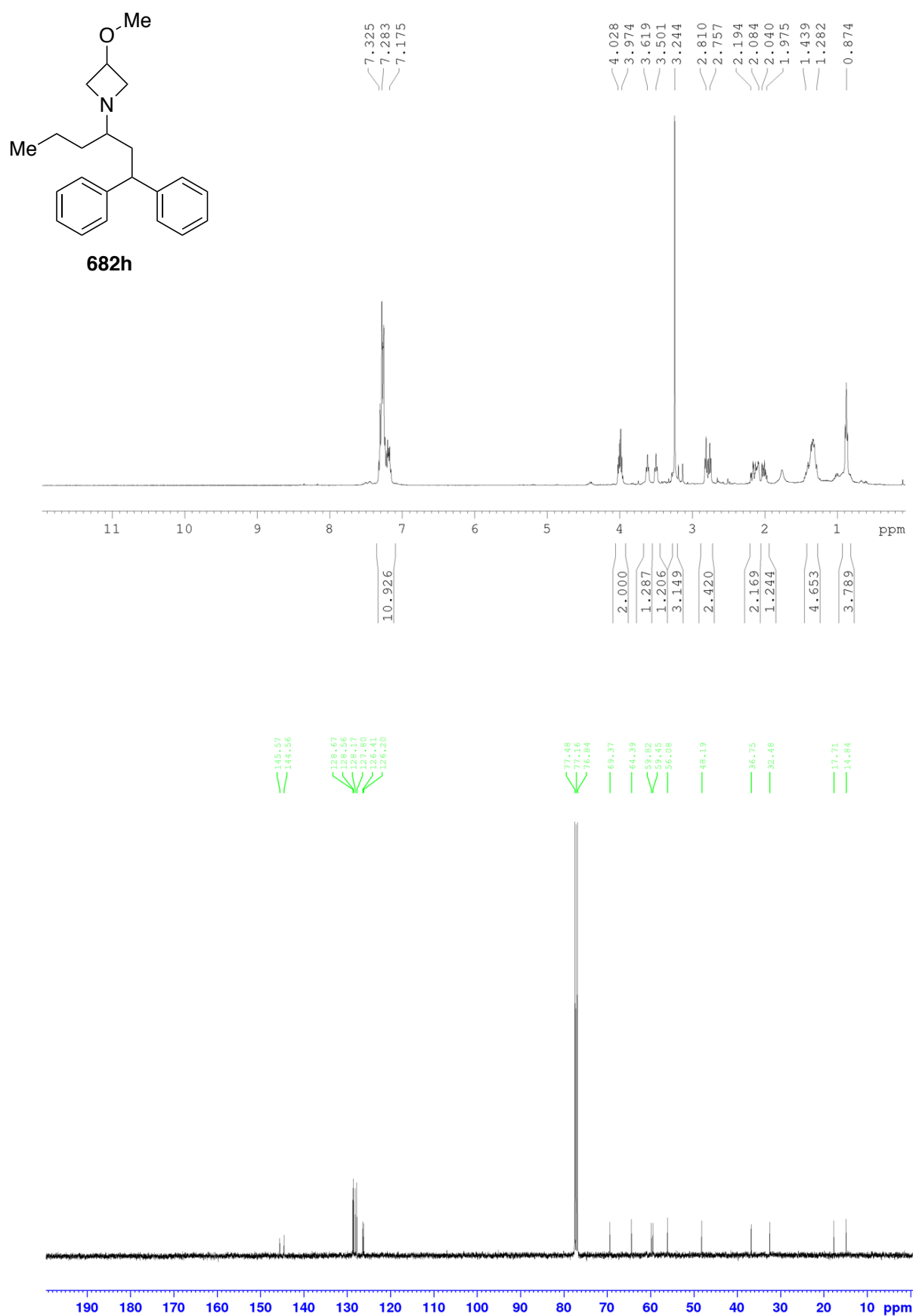


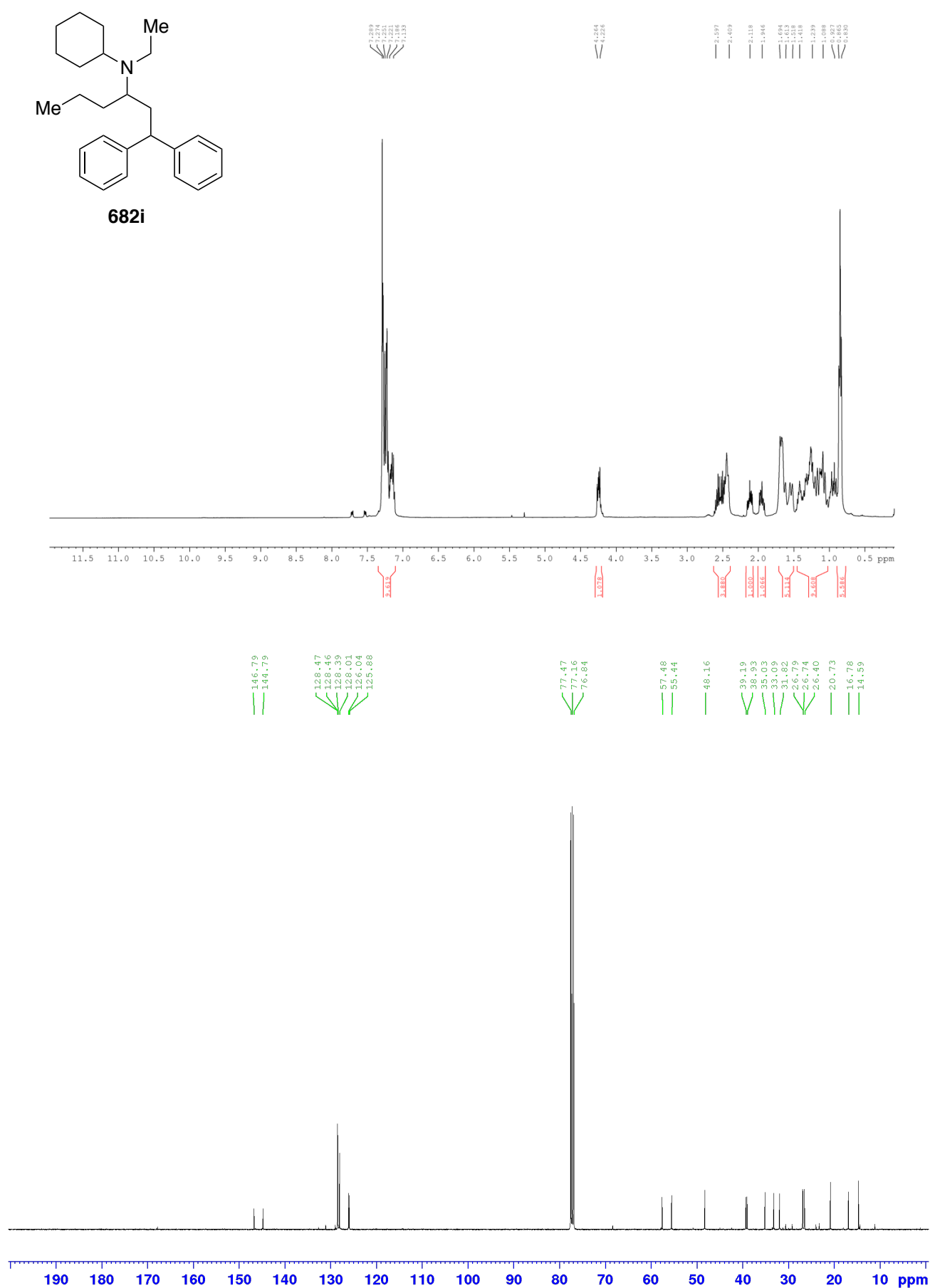


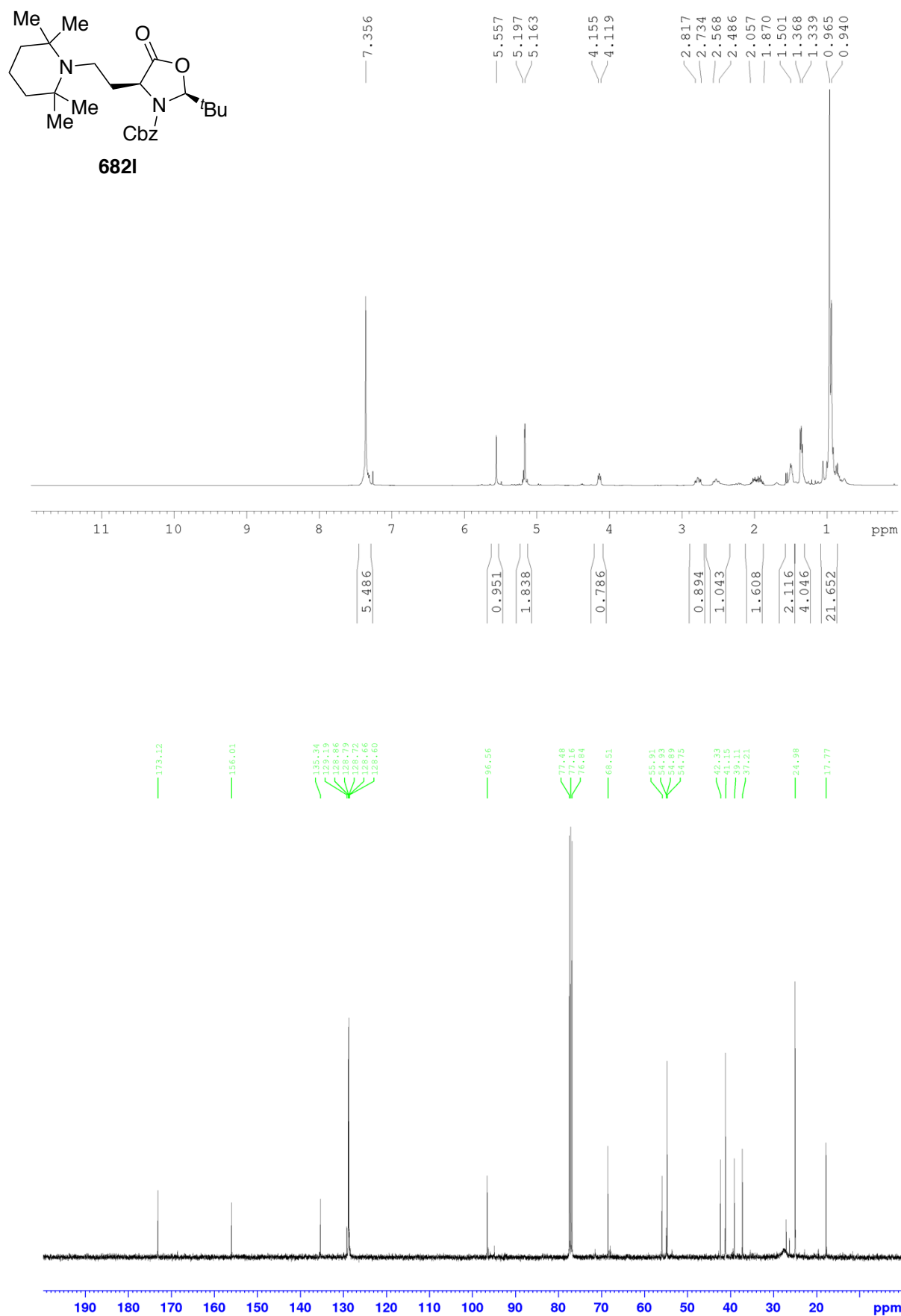


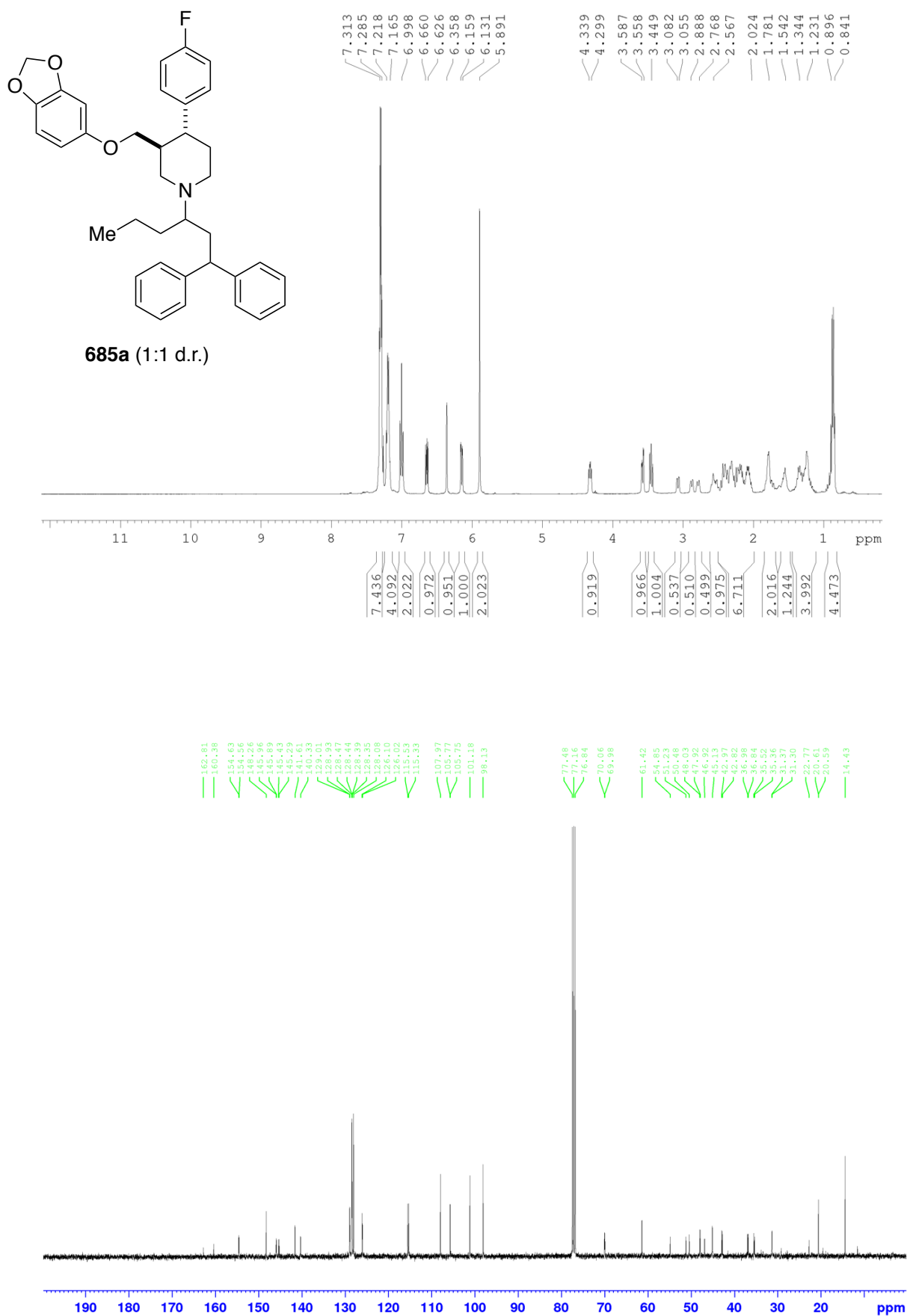


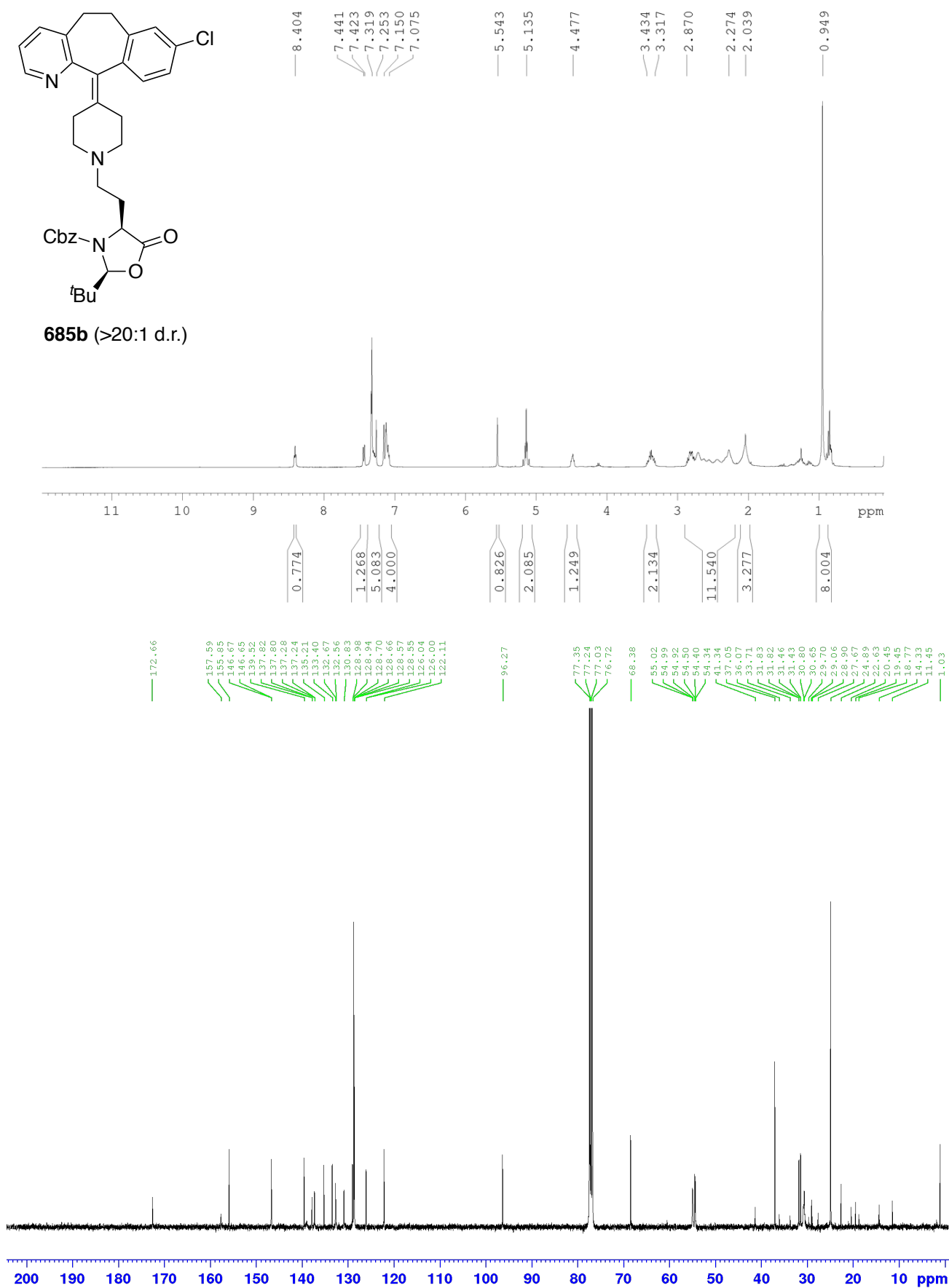


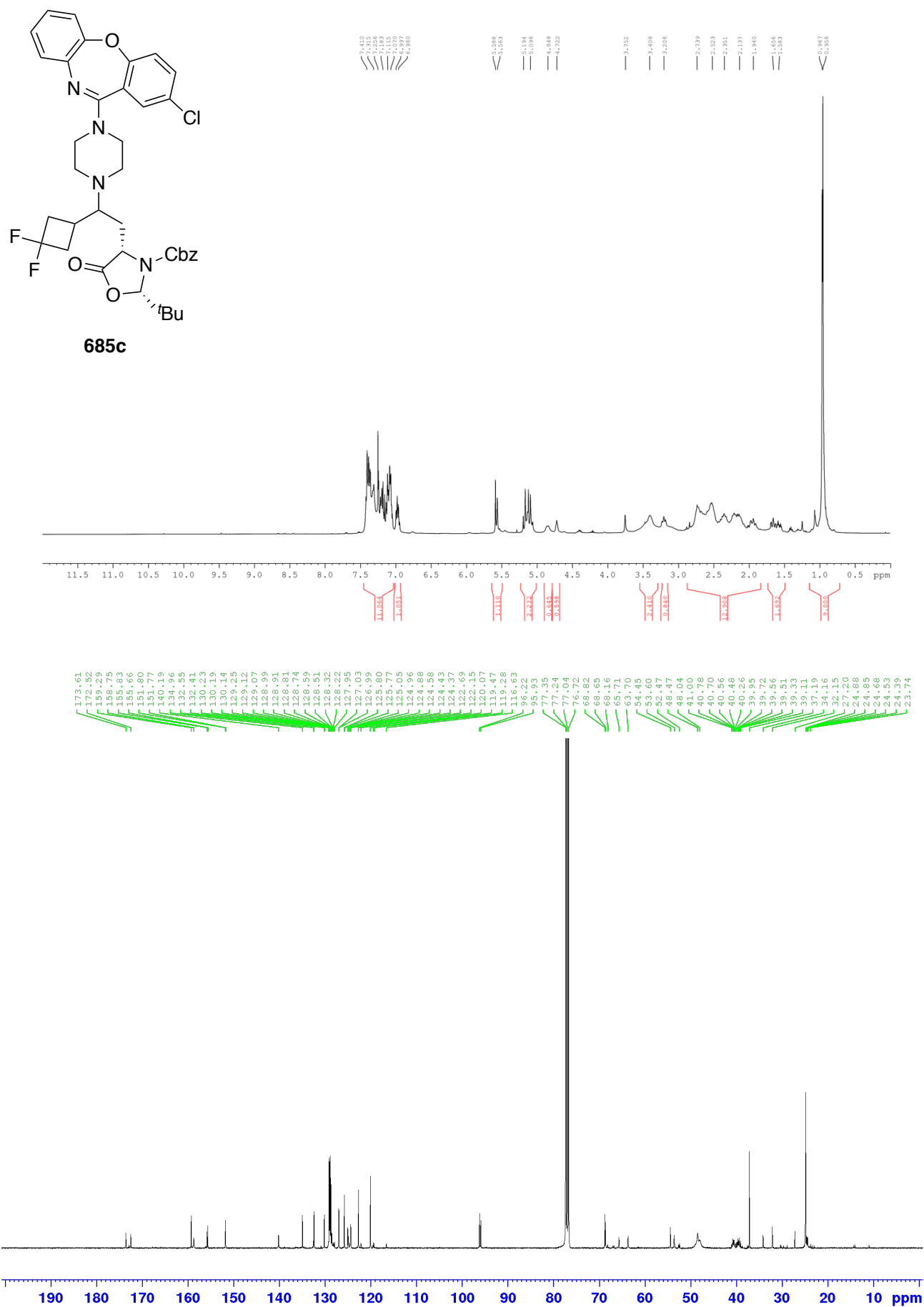




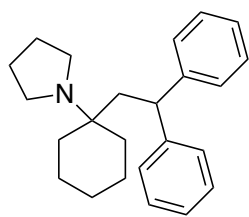












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